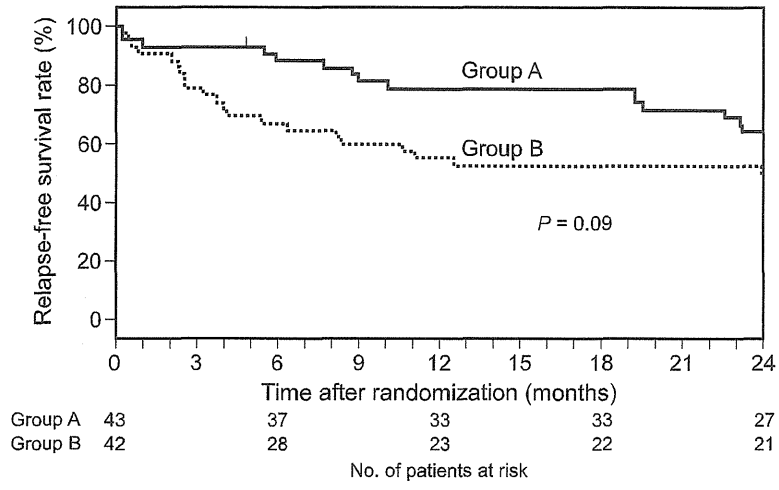

Figure 2. | Relapse-free survival probability (Kaplan–Meier curves).

Table 3. Relapse rates

Treatment Group	Total Number of Relapses	Duration of Observation (d)	Relapse Rate (per person-yr)	Ratio of Relapse Rates (95% Confidence Interval)	*P* Value
Group A	34	30,259	0.41	0.43(0.19 to 0.84)	0.0
Group B	66	25,490	0.95		

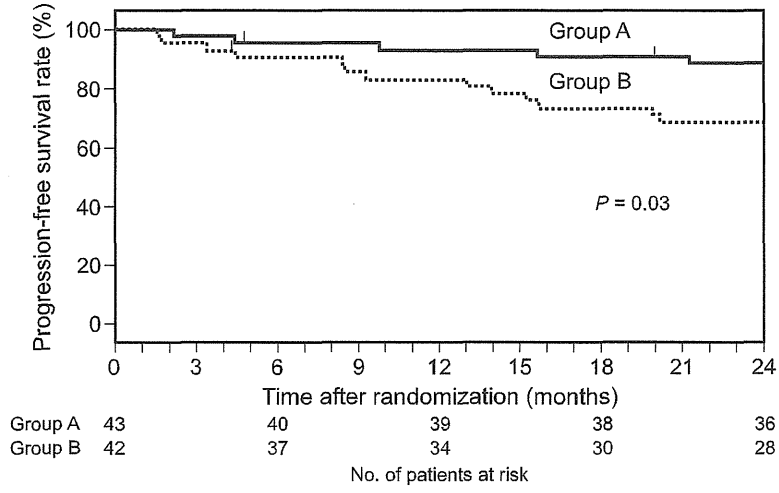

Figure 3. | Progression-free survival probability (Kaplan–Meier curves).

A summary of other adverse events reported during the trial is shown in Table 4. We report cumulative events that occurred within 24 months after randomization, because this time point is when all participants had had an equal opportunity to have an event. The rate and severity of adverse events were similar in both treatment groups. Three patients in group A and two patients in group B had grade III adverse events requiring hospitalization, including one patient in group A who discontinued protocol treatment because of posterior reversible leukoencephalopathy syndrome (25) (month 20), which recovered completely after discontinuation of the protocol treatment. Two of the patients in group A and both of the patients in group B subsequently recovered and restarted protocol treatment as recommended by a physician (Table 4).

Table 4. Summary of adverse events that occurred within 24 months after randomization

Event	Group A (n=43) n (%)	Group B (n=42) n (%)
Grade 3 adverse events		
Pneumonia[a]	3[b,c,d] (7.0)	1[e] (2.4)
Encephalopathy[a]	1[c] (2.3)	1[f] (2.4)
Posterior reversible encephalopathy syndrome[a]	1[b] (2.3)	0
Pneumomediastinum[g]	1[c] (2.3)	0
Grade 1 or 2 adverse events		
Infection[a]	15 (34.9)	13 (31.0)
Asthma[a]	3 (7.0)	1 (2.4)
Edema[a]	1 (2.3)	2 (4.8)
Moon face[a]	3 (7.0)	4 (9.5)
Centripetal obesity[a]	2 (4.7)	1 (2.4)
Hypertrichosis[a]	23 (53.5)	20 (47.6)
Acne[a]	4 (9.3)	2 (4.8)
Cutaneous striae[a]	0	1 (2.4)
Hypertension[g]	7 (16.3)	5 (11.9)
Gingival hyperplasia[g]	4 (9.3)	7 (16.7)
Gastrointestinal event[g]	2 (4.7)	0
Dermatological event[g]	5 (11.6)	3 (7.1)
Neuropsychiatric event[g]	4 (9.3)	3 (7.1)
Pain[g]	0	3 (7.1)
Cataract[g]	2 (4.7)	0
Glaucoma[g]	1 (2.3)	0
Chronic sinusitis[g]	0	1 (2.4)
Cough[g]	1 (2.3)	0
Hyperglycemia[g]	2 (4.7)	2 (4.8)
Hyperkalemia[g]	1 (2.3)	1 (2.4)
Hyperbilirubinemia[g]	2 (4.7)	3 (7.1)
Hyperuricemia[g]	1 (2.3)	1 (2.4)
High-serum glutamic oxaloacetic transaminase[g]	1 (2.3)	3 (7.1)
High-serum glutamic pyruvic transaminase[g]	2 (4.7)	1 (2.4)
High amylase[g]	1 (2.3)	0
High serum creatinine phosphokinase[g]	1 (2.3)	0
Low GFR[g]	1 (2.3)	0
Others[g]	1 (2.3)	3 (7.1)

[a]Multiple reports were recorded for these adverse events.
[b]One patient in group A had pneumonia at month 11 and recovered after 7 days without discontinuing protocol treatment. The same patient had posterior reversible encephalopathy syndrome at month 20, and protocol treatment was discontinued. He recovered completely after 10 days.
[c]One patient in group A had pneumonia, encephalopathy, and pneumomediastinum after influenza infection at month 5 and recovered after 7 days. Protocol treatment was restarted after the recovery.
[d]One patient in group A had pneumonia at month 21 and recovered after 12 days without discontinuing protocol treatment.
[e]One patient in group B had pneumonia at month 5 and recovered after 7 days without discontinuing protocol treatment.
[f]One patient in group B had encephalopathy after rotavirus infection at month 1 and recovered after 7 days. Protocol treatment was restarted after the recovery.
[g]Only the first occurrence of these adverse events was recorded.

Discussion

This study is the first to attempt to select better C_2 levels of cyclosporine in the form of mCyA for FRNS in children. The SRR in group A was 14.4% higher than the SRR in group B, which was larger than the decision threshold of 8%. Also, there was no difference between the two groups with respect to the frequency and severity of adverse events. Therefore, we considered that the C_2 monitoring regimen for group A, in which the target C_2 level was 600–700 ng/ml for the first 6 months and 450–550 ng/ml for the next 18 months, was better than the regimen for group B, in which the target C_2 level was 450–550 ng/ml for the first 6 months and 300–400 ng/ml for the next 18 months. Referencing the report by Ushijima *et al.* (26) on the pharmacokinetic profile of Japanese nephrotic syndrome children treated with mCyA, the mean C_0 levels for months 7–24 in group A might have ranged from 60 to 80 ng/ml, which was lower than the levels in the previous studies (7).

We found that the rate of relapse of nephrotic syndrome was significantly lower in group A than group B patients. This finding agrees with a previous finding that FRNS patients with higher C_2 levels at month 1 tend to have lower relapse rates during cyclosporine treatment (9).

In the previous studies of mCyA treatment by C_2 monitoring for childhood FRNS, the mean relapse rates varied from 0.2 to 1.5 per year under the mean C_2 levels, which ranged from 497.8 to 729.0 ng/ml (13,16,18,20). The relapse rate in group A in the present study (0.41/person-year) was not inferior to the relapse rates in previous studies. Therefore, we considered that the regimen with C_2 target for group A is acceptable for the treatment for childhood FRNS. However, it remains to be elucidated whether the regimen is also acceptable for other populations, because most of C_2 monitoring studies for childhood FRNS were carried out in Japan.

Several grade III adverse events were reported in both groups in this trial. However, all patients with those severe adverse events recovered completely, and most patients restarted protocol treatment. Therefore, we considered adverse events in this trial acceptable. In the present study, two patients (4.7%) in group A developed mild to moderate chronic cyclosporine nephrotoxicity, and zero patients in group B developed this condition. Although the reason is unclear, the prevalence of chronic cyclosporine nephrotoxicity in the present study was much lower than the prevalence in a previous study (discussed in Supplemental Appendix) (15), suggesting that the regimens used in the present study were safe with respect to the development of this condition. The two patients who developed cyclosporine nephrotoxicity both had 9-month AUC levels that seemed to be notably higher than the mean for group A (Supplemental Table 4). However, it is premature to make a conclusion that the higher 9-month AUC levels were responsible for the nephrotoxicity, because the number of patients who developed chronic cyclosporine nephrotoxicity was very low.

One limitation of our study is that, at one particular center, C_2 levels were not measured in most patients. Because we had defined the full analysis set as registered patients whose treatments were correctly started in the protocol, the steering committee considered that center to be ineligible and decided that all eight patients at the center should be excluded from the full analysis set.

Another limitation is that the mean C_2 levels during the first 6 months in group A did not reach the target range, suggesting that it is difficult to control C_2 levels in children, especially when the C_2 target is relatively high. We speculate that a slight difference in dose of mCyA may induce a relatively large difference in C_2 concentrations in children when the C_2 target is relatively high. Nevertheless, the mean C_2 levels in group A were significantly higher than the mean C_2 levels in group B throughout the trial. In addition, the levels of AUC_{0-4} at months 3 and 9 were significantly higher in group A than group B. We, therefore, conclude that patients in both groups were treated in accordance with the protocol. Additional discussion on the target C_2 levels for phase III trials is in Supplemental Appendix.

It is still controversial whether C_2 or C_0 monitoring is better for renal transplant recipients (10,11,27–34). It is also unclear whether C_2 or C_0 monitoring is better for children with FRNS treated with mCyA. Although our study shows that C_2 monitoring with the target C_2 set for group A is promising, phase III trials are required to compare the efficacy and safety of the regimen with the efficacy and safety of the JSPN-recommended C_0 monitoring protocol.

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Physicians who participated in the Japanese Study Group of Kidney Disease in Children 03 are listed in Supplemental Appendix.

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SUPPLEMENTARY APPENDIX

SUPPLEMENTRY TEXT

Pre-study calculation of sample size

The sustained remission rate (SRR) at 24 months in Group B was assumed to be approximately 60%, and the difference in SRR between the two groups was expected to be 15%. If the true difference in SRR between the two groups was indeed at least 15%, then there was a 75% chance of selecting Group A, given the total sample size of 100. The probability that the SRR in Group A was higher than that in Group B was over 90%. The statistical power of this study to reach the significant difference between the groups was 36% under the assumption described above.

Method of randomization

Randomization of the patients into two groups was performed in a 1:1 ratio with a dynamic balancing method, with stratification by site, sex, renal biopsy findings, and duration of disease, to minimize differences in the distribution of baseline variables between the two groups. Dynamic allocation is otherwise known as covariate-adaptive randomization or minimization [S1]. The probability of being assigned to a group varies in order to minimize covariate imbalance.

How to determine the target C_2 levels

We reported an effective and safe treatment protocol for mCyA titrated by monitoring the whole-blood trough level (C_0) in children with FRNS. [9 in the text] In this study, patients received mCyA in a dose that maintained C_0 between 80-100 ng/ml of cyclosporine during the first 6 months, and the dose was adjusted to maintain a level between 60-80 ng/ml for the next 18 months. The probability of relapse-free survival at month 24 was 58.1 %, and mild chronic cyclosporine nephrotoxicity was detected in only 8.6% of patients who underwent renal biopsy after 24 months of treatment. Therefore, we concluded that this regimen is effective and safe. In this trial, mean C_2

levels at month 1 was 486.0±203.9 ng/ml, and there was a tendency for patients with higher C_2 levels at month 1 to have lower relapse rates during the treatment. Also, an international consensus statement on patient management by mCyA C_2 monitoring described that the C_2 target used for maintenance phase adult kidney transplantation was 800 ng/ml. Based on these previous results, we consider that 24 months of treatment for children with FRNS by mCyA C_2 monitoring with a C_2 target between 300 and 700 ng/ml should be effective and safe. However, it is still unclear whether a higher C_2 target or a lower C_2 target within this range is more effective and safer. Therefore, the C_2 target was set to 600-700 ng/ml for the first 6 months and 450-550 ng/ml for the next 18 months for Group A, and it was set to 450-550 ng/ml for the first 6 months and 300-400 ng/ml for the next 18 months for Group B.

Corticosteroid treatment

When patients had relapses of nephrotic syndrome prior to the start of mCyA treatment, they received 2 mg/kg/day of prednisolone, divided into 3 doses (maximum dose of 80 mg/day), until 3 days after obtaining complete remission, or for 4 weeks. This was followed by a single dose of 2 mg/kg (maximum dose of 80 mg/day) of prednisolone in the morning on alternate days for 2 weeks, then 1 mg/kg (maximum dose of 40 mg/day) on alternate days for 2 weeks, and then 0.5 mg/kg (maximum dose of 20 mg/day) on alternate days for 2 weeks. When patients had relapses during mCyA treatment, they received 2 mg/kg/day of prednisolone, divided into 3 doses (maximum dose of 80 mg/day), until 3 days after obtaining complete remission, followed by the same tapering method as described above. No patients received corticosteroids as a maintenance therapy.

Measurement of cyclosporine concentrations and other variables

At week 2 and months 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, and 24 after the start of treatment, we measured the height, weight, and blood pressure of each patient, and collected urine and blood samples from each patient. We measured blood levels of cyclosporine C_2 and the following variables: urinary levels of protein, creatinine, and beta 2 microglobulin; red blood count and white blood

count; blood hemoglobin and urea nitrogen; and serum levels of total protein, albumin, creatinine, sodium, potassium, magnesium, amylase, glutamic oxaloacetic transaminase, and glutamic pyruvic.

At the same time points, estimated glomerular filtration rates were calculated by the Schwartz method. [S2] At months 3 and 9, cyclosporine C_0, C_1, C_3, and C_4 concentrations, as well as C_2 concentrations, were measured by radioimmunoassay using a monoclonal antibody specific for cyclosporine [S3], and AUC_{0-4} values were calculated by the trapezoid method. [S4]

The AUC_{0-4} values and C_2 levels but no other CyA concentrations including C_0 levels at months 3 and 9 were recorded in the case report form.

Discussion on the reason why the prevalence of CyA nephrotoxicity in the present study was lower than that in previous studies

Kengne-Wafo et al. reported that 31 % of steroid-dependent nephrotic syndrome children treated with mCyA with mean C_2 levels of 466 ± 134 ng/ml showed chronic cyclosporine nephrotoxicity.[15 in the Text] The reason why the prevalence of cyclosporine nephrotoxicity in the present study was lower than that in Kengne-Wafo's study is unclear. However, the mean duration of treatment was 4.7 ± 2.0 years before biopsy in Kengne-Walo's study, which was much longer than that in the present study (24 months treatment). Therefore, it is possible the shorter duration of cyclosporine treatment may be due to the lower cyclosporine nephrotoxicity in the present study.

Discussion on the target C_2 levels for phase III trials

As seen in Table S2 and mentioned in "DISCUSSION", it was difficult to control C_2 levels in children, especially when the C_2 target is relatively high. That is probably because 1) As the minimum dose of mCyA capsule is 10 mg, and the concentration of mCyA liquid is 100 mg/ml in Japan, the minimum unit of change in mCyA dose is 10 mg, 2) A slight difference in dose of mCyA induce a relatively large difference in C_2 levels in children when the C_2 target is relatively high.

The mean C_2 levels during the first 6 months in Group A did not reach the target range in our study. However, in approximately 60% of patients in Group A, the mean C_2 levels during the first 6

months were higher than the upper limit of the target C_2 level of Group B (550 ng/ml). We are afraid that true mean C_2 levels will be lower than the target C_2 level if the target C_2 level is decreased (for example, between 550 and 650 ng/ml).

Collectively, we recommend the C_2 monitoring regimen for Group A (C_2 target level: between 600 and 700 ng/ml for the first 6 months, and between 450 and 550 ng/ml for the next 18 months) for phase III trials to compare the efficacy and safety of the regimen those of the JSPN-recommended C_0 monitoring protocol (the C_0 target was set to 80-100 ng/ml for the first 6 months and 60-80 ng/ml for the next 18 months).

Physicians who participated in JSKDC03

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Table S1. Participating centers.

1. Ashikaga Red Cross Hospital, Ashikaga, Japan
2. Dokkyo Medical University School of Medicine, Tochigi, Japan
3. Fukuoka Children's Hospital and Medical Center for Infectious Diseases, Fukuoka, Japan
4. Hyogo Prefectural Kobe Children's Hospital, Kobe, Japan
5. Japanese Red Cross Society Fukuoka Hospital, Fukuoka, Japan
6. Japanese Red Cross Society Himeji Hospital, Himeji, Japan
7. Kobe University Graduate School of Medicine, Kobe, Japan
8. Kumamoto Chuo Hospital, Kumamoto, Japan
9. National Center for Child Health and Development, Tokyo, Japan
10. National Hospital Organization Saitama National Hospital, Saitama, Japan
11. Tokyo Metropolitan Children's Medical Center, Fuchu, Japan
12. Tokyo Women's Medical University, Tokyo, Japan
13. Wakayama Medical University, Wakayama, Japan
14. Yokohama City University Medical Center, Yokohama, Japan

Table S2. Distribution of exact mean C_2 levels.

Months 1-6	Group A (n=43)		Group B (n=42)	
	n	%	n	%
<300 ng/ml	0	0	0	0
300-400 ng/ml	3	7.0	8	19.1
400<-<450 ng/ml	1	2.3	8	19.1
450-550 ng/ml	14	32.6	19	45.2
550<-<600 ng/ml	10	23.3	4	9.5
600-<700 ng/ml	12	27.8	3	7.1
over 700 ng/mL	3	7.0	0	0

Months 7-24	Group A (n=40)		Group B (n=37)	
	n	%	n	%
<300 ng/ml	0	0	4	10.8
300-400 ng/ml	2	5.0	18	48.7
400<-<450 ng/ml	9	22.5	9	24.3
450-550 ng/ml	25	62.5	4	10.8
550<-<600 ng/ml	3	7.5	1	2.7
600-<700 ng/ml	1	2.5	1	2.7
over 700 ng/ml	0	0	0	0

Table S3. Actual dosage of mCyA in the 2 groups.

	Group A				
	n	Mean ± SD (mg/kg/day)	Minimum (mg/kg/day)	Median (mg/kg/day)	Maximum (mg/kg/day)
The first dosage	43	3.1 ± 0.8	1.8	3.0	5.3
Months 1 - 3	43	5.0 ± 1.2	2.7	4.9	7.6
Month 6	43	4.9 ± 1.2	2.9	4.7	7.7
Month 9	40	4.7 ± 1.2	2.5	4.6	7.1
Months 12 - 24	40	4.9 ± 1.4	2.4	4.6	7.7

	Group B				
	n	Mean ± SD (mg/kg/day)	Minimum (mg/kg/day)	Median (mg/kg/day)	Maximum (mg/kg/day)
The first dosage	42	3.1 ± 0.8	1.7	2.9	5.2
Months 1 - 3	42	4.2 ± 1.1	1.7	4.1	6.9
Month 6	42	4.1 ± 1.1	1.3	4.1	6.9
Month 9	37	3.8 ± 1.0	1.3	3.9	6.1
Months 12 - 24	37	3.8 ± 1.2	1.5	3.7	6.7

Table S4. Chronic cyclosporine nephrotoxicity

Group	Age/sex	Relapses during the study	Progression to FRNS	AUC_{0-4} at month 3 (ng·h/ml)	AUC_{0-4} at month 9 (ng·h/ml)	Renal pathology	
						Arteriolar hyalinosis	Striped fibrosis
A	15/male	No	No	1904	2690	Mild to moderate	Mild
A	12/female	No	No	1934	2003	No	Mild

FRNS, frequently relapsing nephrotic syndrome; AUC_{0-4}, area under the concentration-time curve during the first 4 h after treatment with cyclosporine

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Safety of oseltamivir in infants less than one year old: Prospective surveillance during the 2004–2005 influenza season in Japan

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Abstract. The aim of this study was to investigate the treatment of influenza and safety of oseltamivir in infants less than 1 year of age. All-patient surveillance was conducted using centralized enrolment at 219 medical institutions. Safety data were collected for 1,663 patients less than 1 year of age who developed influenza during the 2004–2005 influenza season. Patients were stratified into three groups: patients not treated with a drug (Group A), patients treated with oseltamivir (Group B), and patients treated with a drug other than an antiviral agent (Group C). Significant differences ($P = 0.0074$, $P < 0.0001$) were observed among incidences of adverse events in the three groups (Group A: 26.7%, Group B: 30.0%, Group C: 21.5%) and between the incidences of adverse drug reactions (ADRs) in the two drug-treated groups (Group B: 6.7%, Group C: 0.9%). The most commonly reported ADRs in patients treated with oseltamivir were diarrhoea, hypothermia, vomiting, and rash. We found that 77.2% of patients received oseltamivir and 20.0% received symptomatic treatments such as antipyretic agents. In infants less than 1 year of age, incidence of ADRs with oseltamivir treatment was higher than with symptomatic treatments, however these ADRs were treatable symptoms and consistent with the ADRs reported in young children treated with oseltamivir.
Our analysis of the safety of oseltamivir in infants less than 1 year of age revealed clinical acceptance of safety issues.

Keywords: Infant, under one year old, oseltamivir, influenza virus, drug safety

1. Introduction

Our impetus for studying actual treatment practice for influenza in infants less than 1 year old was the FDA's announcement on its website in December 2003 that oseltamivir (Tamiflu®, oseltamivir phosphate) should not be administered to infants less than 1 year of age due to lack of clinical data and a 1000 mg/kg oral dose of oseltamivir that had been lethal in 7-day-old rats (Roche [F. Hoffmann-La Roche Ltd, Basel, Swiss Confederation]), which in 2007 was reported to have been based on incorrect laboratory data. In 2003, influenza diagnostic kits were readily available in Japan, and influenza virus infection was easily diagnosed. The anti-influenza agents oseltamivir and zanamivir were commonly prescribed for

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influenza virus infection. Oseltamivir was indicated overseas for treatment or prophylaxis of infection with influenza virus types A or B in patients at least 1 year old. However, oseltamivir was indicated in Japan for treatment or prophylaxis of infection with influenza virus types A or B without age restriction, which enabled physicians in Japan to prescribe oseltamivir, at their discretion, to patients less than 1 year of age. Many pediatricians prescribe oseltamivir mainly because of higher incidence of encephalitis and severity of influenza infection in this age group. Given the situation in Japan, the FDA announcement caused great confusion among Japanese pediatricians who felt patients less than 1 year old did not seem to experience the major neurological events described by the FDA.

We therefore conducted a retrospective, on-site, all-patient registry surveillance study to verify the safety of oseltamivir in infants less than 1 year old who were given oseltamivir to treat influenza virus infection in the 2003–2004 influenza season [1]. In this retrospective study, 834 patients were enrolled from 165 sites, and safety was analyzed for 771 patients from 157 sites (43 hospitals and 114 clinics).

The incidence of adverse events (AEs) was 5.3% (41 of 771 patients) and the incidence of adverse drug reactions (ADRs) was 3.2% (25 of 771 patients). A total 51 AEs were reported in 41 patients, and the most commonly reported AEs were gastrointestinal disorders (2.5% [19 of 771 patients]), with commonly reported AEs including diarrhoea (1.9% [15 of 771 patients]) and vomiting (0.8% [6 of 771 patients]). Also, the most commonly reported ADRs were gastrointestinal disorders, and ADRs comprised diarrhoea (1.7% [13 of 771 patients]); vomiting (0.6% [5 of 771 patients]); loose stools and hypothermia (each, 0.3% [2 of 771 patients]); and excitability, bad mood, lethargy, somnolence, rash, papular rash, alanine aminotransferase increased, and aspartate aminotransferase increased (each, 0.1% [1 of 771 patients]). Serious AEs occurred in 4 patients, with convulsion (including febrile convulsion) in 3 patients and respiratory failure in 1 patient. The outcome was death in the patient with respiratory failure.

All AEs were symptoms known to be triggered by influenza virus infection in children or by pyrexia. Only excitability, bad mood, lethargy, and somnolence (one event each) were reported as central nervous system ADRs. Because the reported neurological events are symptoms commonly observed in the natural course of influenza infection, we felt that there was no particular safety issue with oseltamivir in infants less than 1 year old. However, the AE details from this study were retrospectively collected only from medical charts or the memories of the infants' guardians, and we could not fully assess the clinical courses. We therefore decided to conduct a prospective study to acquire and definitively assess AE details. This prospective surveillance study was conducted in infants less than 1 year of age with influenza in the 2004–2005 influenza season. Our findings are reported herein.

2. Materials and methods

2.1. Patients

Infants less than 1 year of age who were suspected of having influenza during the 4-month period from December 2004 to March 2005 were examined at a medical institution specializing in pediatrics. The attending pediatrician used a rapid diagnostic kit for influenza and/or the patient's clinical symptoms (e.g., pyrexia, cough, and nasal symptoms) to confirm a diagnosis of influenza. Any anti-influenza agents used were administered within 48 hours of symptom onset. Pediatricians at 219 institutions (198 clinics and 21 hospitals) who are members of either the Society of Ambulatory and General Pediatrics of Japan or the Japanese Society for Pediatric Infectious Diseases participated in the study. These institutions were spread across 43 of the 47 Japanese prefectures. Pediatricians at 44 of the institutions (40 clinics and 4 hospitals) that participated in the retrospective study also participated in this study.

2.2. Methods

In this surveillance study, all patients less than 1 year of age with influenza were centrally enrolled irrespective of whether an antiviral agent was used for treatment.

In Japan, the approved indication for oseltamivir was the treatment of infection with influenza virus types A or B; there was no age restriction (oseltamivir is now also indicated for prophylaxis). Pediatricians in Japan, at their discretion, would administer anti- influenza agents even in infants less than 1 year of age if influenza virus infection was diagnosed using a rapid

test kit or other method and administration of an anti-influenza agent was judged to be appropriate. When using oseltamivir in infants less than 1 year old, pediatricians administered Tamiflu® Dry syrup at 2 mg/kg b.i.d. for five days, the approved pediatric dosage in Japan.

In this study, decisions on influenza treatment methods for infants less than 1 year of age were entrusted to each child's pediatrician. Methods chosen comprised non-drug symptomatic treatment (e.g., cooling with icepacks), symptomatic treatment with antipyretics or other drugs, and antiviral therapy with anti-influenza agents. Patients treated with antiviral therapy using anti-influenza agents included those given only an anti-influenza agent and those given a concomitant antipyretic or other drug. Anti-influenza agents were administered according to each agent's package insert.

Patients were stratified into three groups according to treatment style: patients not treated with a drug (Group A), patients treated with oseltamivir (Group B), and patients treated with a drug other than an antiviral agent (Group C).

After performing a medical examination, physicians enrolled suitable patients for surveillance by entering their information on an "Enrolment Form", which was to be faxed to an enrolment office "by the day following the diagnosis of influenza".

The physician was to explain surveillance objectives to the guardians or family members who gave consent. These guardians or family members were asked to observe and record their child's condition by filling in a "Symptom Observation Form" during treatment.

Gender, age, body weight, vaccination status, body temperature, virus type (result of antigen detection kit test), and date and time of fever or symptom onset were recorded at the first clinic or hospital visit.

The guardians or family members were asked to monitor their child for symptoms for four weeks after starting treatment. During the first week, guardians or family members were to record their child's body temperature every morning and evening, the severity of influenza symptoms such as nasal symptoms and cough, and any other symptoms of concern. Thereafter, they were to record body temperature once a week and any symptoms of concern. The child's pediatrician was then to decide whether each symptom was an AE or ADR on the basis of details in the returned "Symptom Observation Form", and to enter the relevant data in the patient's case report form. If a "Symptom Observation Form" was not returned, the pediatrician checked for occurrences of AEs by contacting the child's guardian or family member by telephone.

The observation period in this study was four weeks, and all events that occurred during this period were collected as adverse events. Therefore, events were handled as adverse events even for re-infection cases.

The enrolment guidelines specified that double-enrolments of the same case would not be accepted.

Each case was also examined by a third party to evaluate the appropriateness of the pediatrician's assessment.

2.3. Statistical analysis

The Student unpaired t test or the chi-square test was used to compare patient baseline characteristics and the incidences of AEs and ADRs among groups A, B, and C. The Steel-Dwass test was used for multiple comparison. A significant difference was regarded as being a P value less than 0.05.

3. Results

In this study, 1,771 patients from 219 institutions were enrolled. Of these patients, 108 were excluded from the safety analysis set. Excluded patients comprised 47 patients with indeterminate AEs, 30 transferred from another institution, 14 re-enrolled upon re-infection, 11 given zanamivir, 4 not enrolled during the enrolment period, and 2 not less than 1 year of age. The safety analysis set therefore comprised 1,663 enrolled patients from 219 institutions (198 clinics and 21 hospitals).

At least 98% of patients were treated with a drug, and oseltamivir accounted for the highest proportion of drugs used, 77.2%.

The baseline characteristics of enrolled patients are presented in Table 1. In the safety analysis set, the mean age was 7.9 ± 2.5 months (21–365 days), the mean body weight was 8.3 ± 1.3 kg (3.6–13.2 kg), the mean time from influenza onset to diagnosis was 1.7 ± 0.8 days (1–9 days), and the mean body temperature at examination was 38.5 ± 0.7°C (36.0–41.1°C). The age of 82.0% of patients (1,364 of 1,663 patients) was more than 6 months, days from influenza onset to diagnosis for 89.8% of patients (1,494 of 1,663 pa-

Table 1a
Patient baseline characteristics
Baseline characteristics in influenza-infected infants less than one year of age in each treatment group

		Treatment group		
		Group A	Group B	Group C
		Number of patients (% of patients)		
Number		$n = 30$	$n = 1,284$	$n = 349$
Gender	Female	12 (40.0)	582 (45.3)	161 (46.1)
	Male	18 (60.0)	702 (54.7)	188 (53.9)
Age	0–2 months	6 (20.0)	14 (1.1)	19 (5.4)
	3–5 months	7 (23.3)	166 (12.9)	87 (24.9)
	6–8 months	8 (26.7)	424 (33.0)	115 (33.0)
	9–11 months	9 (30.0)	680 (53.0)	128 (36.7)
Body weight	< 8 kg	13 (43.3)	385 (30.0)	148 (42.4)
	8 to < 11 kg	13 (43.3)	848 (66.0)	181 (51.9)
	⩾ 11 kg	1 (3.3)	31 (2.4)	4 (1.1)
	Unknown	3 (10.0)	20 (1.6)	16 (4.6)
Vaccination	No	27 (90.0)	1,183 (92.1)	332 (95.1)
	Yes	1 (3.3)	68 (5.3)	8 (2.3)
	Unknown	2 (6.7)	33 (2.6)	9 (2.6)
Time from onset to diagnosis	Mean ± SD	1.9 ± 0.9	1.7 ± 0.7*	1.9 ± 1.0
	(min–max)(days)	(1–5)	(1–9)	(1–7)
	⩽ 2 days	24 (80.0)	1,173 (91.4)	297 (85.1)
	3 days	5 (16.7)	86 (6.7)	32 (9.2)
	⩾ 4 days	1 (3.3)	21 (1.6)	20 (5.7)
	Unknown	0	4 (0.3)	0
Body temperature (°C)	Mean ± SD	38.1 ± 0.9†	38.5 ± 0.7‡	38.5 ± 0.7§
	(min–max)	(36.3–39.5)	(36.0–41.1)	(36.0–41.1)
	Severe (> 39°C	3 (10.0)	327 (25.5)	54 (15.5)
	Moderate (38–39°C)	16 (53.3)	582 (45.3)	154 (44.1)
	Mild (< 38°C)	6 (20.0)	202 (15.7)	84 (24.1)
	Unknown	5 (16.7)	173 (13.5)	57 (16.3)
Virus type (Result of Rapid test)	A	6 (20.0)	376 (29.3)	116 (33.2)
	B	21 (70.0)	763 (59.4)	215 (61.6)
	A & B		5 (0.4)	
	A or B	3 (10.0)	36 (2.8)	6 (1.7)
	Negative		32 (2.5)	4 (1.1)
	Unknown		72 (5.7)	8 (2.3)

Group A: Patients treated with no therapeutic drugs. Group B: Patients treated with oseltamivir (Tamiflu®). Group C: Patients treated with drugs other than anti-influenza drugs.
* Excluding four patients with unknown number of days to examination. † Excluding five patients with unknown body temperature at examination. ‡ Excluding 173 patients with unknown body temperature at examination. § Excluding 57 patients with unknown body temperature at examination.

tients) was less than 2 days, the body temperature of 68.3% of patients (1,136 of 1,663 patients) was 38°C or higher, and the virus type in 60.1% of patients (999 of 1,663 patients) was type B (reflecting the prevalence of that year). Examination of pediatrician treatment choice by patient age group showed that 77.5% of patients (424 of 547 patients) aged 6 to 8 months and 83.2% of patients (680 of 817 patients) aged 9 to 11 months were treated with oseltamivir. Examination of treatment choice by body weight showed that 69.5% of patients (879 of 1,264 patients) treated with oseltamivir (Group B) weighed more than 8 kg. Examination of treatment choice by body temperature showed that 85.2% of patients (327 of 384 patients) whose body temperature exceeded 39°C were treated with oseltamivir.

Table 1b
Patient baseline characteristics
Baseline characteristics in influenza-infected infants less than one year of age treated with oseltamivir
– Body weight and dose by age –

		0–2 months	3–5 months	6–8 months	9–11months
Number		$n = 14$	$n = 166$	$n = 424$	$n = 680$
Age (month)	Mean ± SD	1.8 ± 0.6	4.4 ± 0.7	7.1 ± 0.8	10.0 ± 0.8
	(Min–Max)	(0–2)	(3–5)	(6–8)	(9–11)
Body weight (kg)	Mean ± SD	5.5 ± 0.8	7.2 ± 0.9*	8.3 ± 1.0†	9.0 ± 1.0‡
	(Min–Max)	(4.4–7.5)	(5.0–11.0)	(5.7–13.0)	(6.0–12.5)
Dose (mg/kg/day)	Mean ± SD	3.6 ± 0.7	3.8 ± 0.6§	3.8 ± 0.4¶	3.8 ± 0.4#
	(Min–Max)	(1.9–4.8)	(1.6–8.2)	(2.0–5.3)	(1.9–7.6)

* Excluding one patient with unknown number of body weight to examination. † Excluding seven patients with unknown body weight at examination. ‡ Excluding 12 patients with unknown body weight at examination. § Excluding two patients with unknown number of dose to examination. ¶ Excluding seven patients with unknown dose at examination. # Excluding 12 patients with unknown dose at examination.

The mean oseltamivir dose was 3.8 ± 0.4 mg/kg/day (min, quartiles, max: 1.6, 3.7, 3.9, 4.0, 8.2). Many patients were given doses slightly less than the 4 mg/kg/day listed in the package insert.

3.1. Incidence of adverse events

The overall incidence of AEs in this study was 28.1% (468 of 1,663 patients). The incidence of AEs was 26.7% (8 of 30 patients) in Group A, 30.0% (385 of 1,284 patients) in Group B, and 21.5% (75 of 349 patients) in Group C. The incidences of AEs by system organ class (SOC) in each treatment group are presented in Table 2. A significant difference ($P = 0.0074$) in incidence of AEs was seen among groups A, B, and C. There was also a significant difference ($P = 0.0037$) between groups B and C (multiple comparison).

The most common AEs by SOC were "infections and infestations" in 14.0% (233 of 1,663 patients), "respiratory, thoracic and mediastinal disorders" in 6.5% (108 of 1,663 patients), "gastrointestinal disorders" in 5.5% (91 of 1,663 patients), "skin and subcutaneous tissue disorders" in 3.7% (62 of 1,663 patients), and "general disorders and administration site conditions" in 3.3% (55 of 1,663 patients). The incidence of serious adverse events (SAEs) was 1.5% (25 of 1,663 patients). The SAEs comprised bronchitis, gastroenteritis rotavirus, pneumonia, convulsions, and asthma (three occurrences each); bronchiolitis and diarrhoea (two occurrences each); and exanthema subitum, influenza, meningitis haemophilus, subdural hygroma, otitis media, acute otitis media, pseudocroup, staphylococcal infection, hypoproteinaemia, encephalitis, vomiting, erythema, and hypothermia (one occurrence each).

One death was also reported. The reported event was encephalitis, and the patient was in Group C. A causal relationship to drug treatment was ruled out by the attending pediatrician.

This study was conducted as surveillance of all patients at each medical institution, but because it was not a randomized comparative study, it must be noted that severity differed in each group. If body temperature at initial examination is taken as one indicator of symptom severity, the fact that oseltamivir was used in 85.2% of patients (327 of 384 patients) whose body temperature exceeded 39°C suggests that the attending pediatrician's choice of treatment was based on the patient's condition on examination. There was an uneven distribution of patients among the groups, with only 30 patients in the group that did not receive any treatment. Although there was a high incidence of AEs in patients treated with oseltamivir, the results of this study were inconclusive as to whether AE incidence increases with oseltamivir treatment.

3.2. Incidence of adverse drug reaction

The ADRs are listed in Table 3. The incidence of ADRs in this study was 6.7% (86 of 1,284 patients) in Group B and 0.9% (3 of 349 patients) in Group C. A significant difference ($P < 0.0001$) was observed between these two treatment groups.

The most common ADRs seen in patients treated with oseltamivir were diarrhoea (31 occurrences), hypothermia (20 occurrences), vomiting (17 occurrences), and rash (14 occurrences).