MAJOR ARTICLE

Early Oseltamivir Treatment of Influenza in Children 1–3 Years of Age: A Randomized Controlled Trial

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Background. Oseltamivir provides modest clinical benefits to children with influenza when started within 48 hours of symptom onset. The effectiveness of oseltamivir could be substantially greater if the treatment were started earlier during the course of the illness.

Methods. We carried out a randomized, double-blind, placebo-controlled trial of the efficacy of oseltamivir started within 24 hours of symptom onset in children 1–3 years of age with laboratory-confirmed influenza during the seasons of 2007–2008 and 2008–2009. Eligible children received either orally administered oseltamivir suspension or a matching placebo twice daily for 5 days. The children received clinical examinations, and the parents filled out detailed symptom diaries for 21 days.

Results. Of 408 randomized children who received the study drug (oseltamivir, 203, and placebo, 205), 98 had laboratory-confirmed influenza (influenza A, 79, and influenza B, 19). When started within 12 hours of the onset of symptoms, oseltamivir decreased the incidence of acute otitis media by 85% (95% confidence interval, 25%-97%), but no significant reduction was observed with treatment started within 24 hours. Among children with influenza A, oseltamivir treatment started within 24 hours shortened the median time to resolution of illness by 3.5 days (3.0 vs 6.5 days; $P = .002$) in all children and by 4.0 days (3.4 vs 7.3; $P = .006$) in unvaccinated children and reduced parental work absenteeism by 3.0 days. No efficacy was demonstrated against influenza B infections.

Conclusions. Oseltamivir treatment started within 24 hours of symptom onset provides substantial benefits to children with influenza A infection.

Clinical trials registration. ClinicalTrials.gov identifier: NCT00593502.

Influenza places a great burden of illness on children, whether measured by annual attack rates, outpatient visits, or hospitalizations [1–7]. The impact of influenza is not limited to the viral infection, because influenza frequently predisposes children to bacterial complications, such as acute otitis media [7–11]. Children were affected extensively during the recent 2009 A/H1N1 pandemic, and pediatric deaths attributable to influenza are not infrequent [12, 13].

Oseltamivir remains the only recommended antiviral drug for treating influenza in children <5 years of age [14, 15]. The evidence for the effectiveness of oseltamivir in previously healthy children of this age, however, is limited to one randomized controlled trial, in which treatment started within 48 hours of the onset of symptoms reduced the duration of illness by 1.5 days and the incidence of influenza-associated acute otitis media by 44% in children 1–12 years of age [10]. In the absence of further studies, a recent meta-analysis concluded that neuraminidase inhibitors provide only a small benefit in children by shortening the duration of illness by 0.5–1.5 days [16].

The mechanism of action of oseltamivir, the pathogenesis of influenza, and previous studies of oseltamivir in adults suggest that the effectiveness of oseltamivir in children could be substantially greater if the treatment were started earlier than within 48 hours of the appearance of symptoms [14, 17]. We determined

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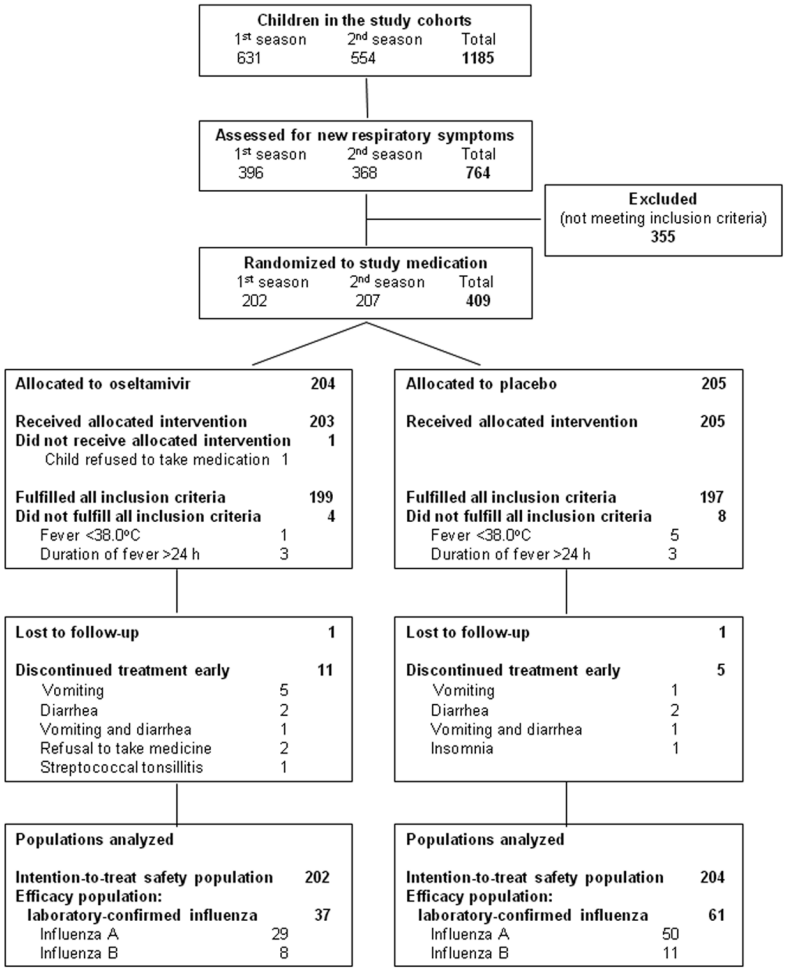

Figure 1. Flow chart of the randomized controlled trial of early oseltamivir treatment of influenza in children 1–3 years of age.

the clinical efficacy of oseltamivir treatment started within 24 hours of symptom onset in children 1–3 years of age with laboratory-confirmed influenza.

METHODS

Study Design

This randomized, double-blind, placebo-controlled, investigator-initiated trial was performed at a single primary care study clinic in Turku, Finland, during the influenza seasons of 2007–2008 (predominance of A/H1N1 strains) and 2008–2009 (predominance of A/H3N2 strains). The study was approved by the Ethics Committee of the Hospital District of Southwest Finland, and it was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 1983). Written informed consent was obtained from the parents of all children. The trial was registered with ClinicalTrials.gov (NCT00593502).

Participants

Before each influenza season, children 1–3 years of age were recruited into cohorts ($n = 631$ in 2007–2008 and $n = 554$ in 2008–2009) by mailed announcements and local advertisements. No exclusion criteria were used for enrollment. When active local viral surveillance indicated that influenza viruses were starting to circulate, a study clinic was opened, and the parents were asked to bring the child to the clinic whenever the child had fever or signs of respiratory infection. The study clinic was open daily from January 14 through April 9, 2008, and from January 7 through March 26, 2009 (8:00 AM–8:00 PM during weekdays and 9:00 AM–6:00 PM during weekends). During each visit, the signs and symptoms of the child were recorded on a structured form, and the child was examined by a physician to assess the eligibility of the child to participate in the treatment trial. To be eligible, the child had for <24 hours a fever (oral, rectal, or axillary temperature ≥38.0°C) and ≥1

Table 1. Baseline Characteristics, According to Study Group, of the 98 Children with Confirmed Influenza Infection

Characteristic	Oseltamivir (n = 37)	Placebo (n = 61)	Total (n = 98)	P
Age, mean ± SD, years	2.3 ± 0.8	2.5 ± 0.8	2.4 ± 0.8	.35
Age category				
1 to <2 years	18 (48.6)	19 (31.1)	37 (37.8)	.08
2 to <3 years	9 (24.3)	23 (37.7)	32 (32.7)	.17
3 to <4 years	10 (27.0)	19 (31.1)	29 (29.6)	.66
Sex				
Female	14 (37.8)	23 (37.7)	37 (37.8)	.99
Male	23 (62.2)	38 (62.3)	61 (62.2)	.99
Day care attendance	16 (43.2)	32 (52.5)	48 (49.0)	.50
Preterm birth	5 (13.5)	3 (4.9)	8 (8.2)	.15
Diagnosis of asthma	2 (5.4)	2 (3.3)	4 (4.1)	.63
Influenza vaccination for the season	3 (8.1)	10 (16.4)	13 (13.3)	.36
Presenting symptoms				
Highest fever before randomization, mean ± SD, °C	38.9 ± 0.5	38.9 ± 0.6	38.9 ± 0.5	.79
Rhinitis	27 (73.0)	51 (83.6)	78 (79.6)	.21
Cough	28 (75.7)	44 (72.1)	72 (73.5)	.70
Otitis media at baseline	5 (13.5)	6 (9.8)	11 (11.2)	.74
Time from onset of fever to first dose of study medication, mean ± SD, hours	11.1 ± 6.9	8.8 ± 6.6	9.7 ± 6.8	.10

NOTE. Data are no. of children (% of children in that group), unless otherwise indicated. P values are for comparisons between the treatment groups.

sign or symptom of respiratory infection (cough, rhinitis, or sore throat) or a positive rapid influenza test result. Excluded were children with virologically confirmed infection other than influenza, suspicion of serious invasive bacterial infection requiring immediate hospitalization, poorly controlled underlying medical condition, known immunosuppression, allergy to oseltamivir, oseltamivir treatment within the preceding 4 weeks, or participation in another clinical trial with an investigational drug.

Randomization and Treatment Assignment

The randomization, labeling, and packaging of the study drugs were performed by Hoffmann-La Roche. The treatments were randomized in blocks of 4 with an allocation ratio of 1:1. The study drugs were forwarded to the investigators in individually sealed and consecutively numbered packages. In consecutive order of study entry, eligible children were given the next available package of medication that contained either orally administered oseltamivir suspension or a matching placebo. The study drugs were administered twice daily for 5 days (total of 10 doses). The dosage of oseltamivir was 30 mg twice daily for children weighing ⩽15.0 kg and 45 mg twice daily for children weighing 15.1–23.0 kg. In most cases, the first dose was given at the study clinic, but in some cases the parents chose to give the first dose at home but always within 24 hours of the onset of fever. The parents were advised to give the child relief medication (antipyretics and/or analgesics) as needed. A child was regarded as adherent if he or she had received ⩾8 doses or 80% of the designated amount of the drug.

Study Procedures

After the initial visit, a follow-up clinical examination was scheduled on days 5–8. In addition, the parents were asked to bring the child to the clinic any time they deemed it necessary, and especially if they suspected the development of acute otitis media or any other complications. Nasal swab samples for viral detection were obtained during all visits if the child was symptomatic. Acute otitis media was diagnosed by signs of inflammation of the tympanic membrane, the presence of middle-ear effusion as detected by pneumatic otoscopy, and ⩾1 sign of acute infection. In addition to pneumatic otoscopy, tympanometry and spectral-gradient acoustic reflectometry were used in diagnosing acute otitis media during each visit. A chest radiograph was obtained if pneumonia was suspected. All visits were free of charge.

The parents filled out symptom diaries twice daily on days 1–7 and once daily on days 8–21. At each time point, the parents recorded the child's measured temperature; presence and severity (4-point scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe) of symptoms (cough, rhinitis, vomiting, diarrhea, or any other symptom); child's return to normal activities; child's absence from day care; parental absence from work because of child's illness; and administration of the study drug, any relief medications, or antibiotics.

Table 2. New Episodes of Acute Otitis Media (AOM) Developing after the Start of the Study Medication in Children with Confirmed Influenza

Time to start of treatment, subgroup	Oseltamivir		Placebo		Relative risk (95% CI)	Percent relative reduction[a] (95% CI)	*P*
	n	No. (%) of children with AOM	*n*	No. (%) of children with AOM			
Within 24 hours							
Any influenza	37	8 (21.6)	61	19 (31.1)	0.69 (0.34–1.37)	31 (−37 to 66)	.31
Any influenza in unvaccinated children	34	8 (23.5)	51	15 (29.4)	0.80 (0.38–1.62)	20 (−62 to 62)	.55
Influenza A	29	6 (20.7)	50	15 (30.0)	0.69 (0.30–1.50)	31 (−50 to 70)	.37
Influenza A in unvaccinated children	26	6 (23.1)	41	11 (26.8)	0.86 (0.36–1.95)	14 (−95 to 64)	.73
Influenza B	8	2 (25.0)	11	4 (36.4)	0.69 (0.17–2.48)	31 (−148 to 83)	.99
Within 12 hours							
Any influenza	18	1 (5.6)	41	15 (36.6)	0.15 (0.03–0.75)	85 (25 to 97)	.02
Influenza A	14	1 (7.1)	35	12 (34.3)	0.21 (0.04–1.01)	79 (−1 to 96)	.08

NOTE. Five children in the oseltamivir group and 6 children in the placebo group had acute otitis media at baseline and were thus not included in the numbers of children who developed a new acute otitis media. CI, confidence interval.

[a] The percent relative reduction in acute otitis media was defined as (1 − relative risk) × 100.

Virological Methods

During each visit, 3 nasal swab samples were obtained from the child (including children with a positive rapid influenza test) with flocked swabs [18, 19]. The specimens were subjected to viral culture in Madin-Darby canine kidney cells followed by immunoperoxidase staining with monoclonal antibodies and antigen detection by means of time-resolved fluoroimmunoassay [20, 21]. All specimens that remained negative for influenza with these methods were further tested with reverse-transcriptase polymerase chain reaction (RT-PCR) assays. A child was considered to have influenza if any of the specimens tested positive for influenza A or B viruses by any of these methods.

Outcomes

The primary outcome was the development of acute otitis media in children with laboratory-confirmed influenza in whom the treatment was started within 24 hours of the onset of symptoms; this outcome was the only one that was predefined to be analyzed also in the subgroup of children in whom the treatment was started within 12 hours of symptom onset. The main secondary outcome was the time to resolution of illness, defined as the interval from the administration of the first dose of the study medication to the first time when the following conditions were met simultaneously and lasted so for ⩾24 hours: temperature ⩽37.5°C, rhinitis and cough either absent or mild, a healthy appearance, and a return of the child to normal activities. If fever reappeared or if cough or rhinitis worsened to moderate or severe levels during the 5-day study medication, the duration of these symptoms was calculated until the first time that the above listed conditions were met after the worsening of these symptoms. Other secondary outcomes were time to resolution of all symptoms (requiring total absence of cough and rhinitis); resolution of fever (⩽37.5°C); parental absence from work; child's absence from day care; use of relief medications or antibiotics; incidence of complications other than acute otitis media; and hospitalization.

Statistical Analyses

The sample size calculations were based on the assumptions that 50% of children fulfilling the inclusion criteria will have influenza; 30% of influenza-infected children receiving placebo will develop acute otitis media; and oseltamivir treatment will prevent 60% of acute otitis media cases. With a 5% level of significance and 80% power, the number of influenza-infected children needed in each group was 77.

Because oseltamivir cannot be expected to have any effect in infections other than influenza, the efficacy analyses were restricted to children who had a laboratory-confirmed influenza A or B infection with the onset of symptoms within 24 hours and who had received ⩾1 dose of the study drug. The safety of the drug was analyzed in the intention-to-treat population that consisted of all randomized children who had received ⩾1 dose of the study medication and from whom any follow-up information was available.

The χ^2 test or the Fisher exact test was used for comparing differences in proportions; the unpaired *t* test was used for comparing differences in means; and the Mann-Whitney *U* test was used for comparing differences in medians between the groups. The Wilcoxon (survival) test was used for comparing the survival curves in the time-to-event analyses; children who withdrew from the study prematurely were censored at the time of the last assessment—that is, they contributed to the analyses until their withdrawal. All statistical analyses were performed

Table 3. Time to Resolution of Symptoms and Duration of Absenteeism in Different Subgroups of Children with Influenza

Subgroup, outcome	Oseltamivir		Placebo		Difference,[a] days	P[b]
	n	Median days (IQR)	*n*	Median days (IQR)		
Any influenza	37		61			
Resolution of illness		4.3 (2.2–5.9)		5.7 (4.2–10.3)	1.4	.004
Resolution of fever		1.7 (0.9–2.9)		2.9 (1.2–4.7)	1.2	.004
Resolution of all symptoms		10.4 (4.6–12.4)		13.3 (10.3–17.1)	2.8	<.001
Parental absence from work		0.0 (0.0–2.0)		2.0 (0.0–4.0)	2.0	.01
Child's absence from day care		2.0 (1.0–4.0)		4.0 (3.0–5.0)	2.0	.01
Any influenza in unvaccinated children	34		51			
Resolution of illness		4.3 (2.2–6.4)		7.3 (4.2–10.3)	2.9	.009
Resolution of fever		1.8 (1.0–2.9)		3.6 (1.3–4.8)	1.8	.01
Resolution of all symptoms		10.4 (4.6–12.4)		13.3 (10.3–16.2)	2.8	.003
Parental absence from work		0.0 (0.0–2.0)		2.0 (0.0–4.0)	2.0	.02
Child's absence from day care		2.0 (1.0–4.0)		4.0 (3.0–5.0)	2.0	.01
Influenza A	29		50			
Resolution of illness		3.0 (2.2–5.9)		6.5 (4.3–11.1)	3.5	.002
Resolution of fever		1.5 (0.9–2.9)		3.3 (1.6–4.8)	1.8	<.001
Resolution of all symptoms		9.4 (4.4–12.4)		14.0 (11.3–18.0)	4.6	.001
Parental absence from work		0.0 (0.0–2.0)		3.0 (0.0–4.0)	3.0	.007
Child's absence from day care		2.0 (1.0–4.0)		4.0 (3.0–5.0)	2.0	.002
Influenza A in unvaccinated	26		41			
Resolution of illness		3.4 (2.1–6.4)		7.3 (4.6–11.1)	4.0	.006
Resolution of fever		1.7 (1.0–2.9)		3.7 (1.7–4.8)	2.0	.004
Resolution of all symptoms		9.9 (4.4–12.4)		13.3 (10.3–17.1)	3.4	.006
Parental absence from work		0.0 (0.0–2.0)		3.0 (0.0–4.0)	3.0	.01
Child's absence from day care		2.0 (1.0–4.0)		4.0 (3.0–5.0)	2.0	.002
Influenza B	8		11			
Resolution of illness		4.4 (4.1–6.9)		4.7 (3.4–8.3)	0.3	.93
Resolution of fever		2.8 (1.2–3.3)		1.9 (0.8–4.5)	−1.0	.87
Resolution of all symptoms		11.3 (5.2–12.8)		13.2 (7.2–13.3)	1.9	.41
Parental absence from work		1.0 (0.0–3.0)		1.0 (0.0–3.0)	0.0	.97
Child's absence from day care		2.5 (1.0–4.0)		1.5 (1.0–4.0)	−1.0	.70

NOTE. IQR, interquartile range.

[a] Because of rounding to one decimal place, some of the differences may look incorrect, but they have been correctly calculated.

[b] *P* values for the differences in the resolution of illness, fever, and all symptoms between the groups were derived from the survival analyses and calculated with the Wilcoxon (survival) test. *P* values for the differences in absences between the groups were calculated with the Mann-Whitney *U* test.

with SAS, version 9.2 (SAS), or StatsDirect, version 2.7.7 (StatsDirect).

RESULTS

Participants and Influenza Infections

Of 1,185 children enrolled in the follow-up cohorts, 409 were randomized and 408 received an intervention (oseltamivir, 203, and placebo, 205) (Figure 1). Among the 396 children who fulfilled all inclusion criteria, 98 (24.7%) had laboratory-confirmed influenza (influenza A, 79, and influenza B, 19). The mean age of influenza-infected children was 2.4 years, and 13 (13.3%) had received influenza vaccine for the season (Table 1). The diagnosis of influenza was based on viral culture in 85 children (86.7%); 4 children (4.1%) were additionally positive by antigen detection and 9 (9.2%) by RT-PCR. Of a total of 31 subtype A/H1N1 viruses isolated during the 2007–2008 season, 3 (9.7%) were resistant to oseltamivir and showed the typical H274Y mutation; all resistant isolates were from children who received placebo.

Clinical Efficacy

Incidence of acute otitis media. No significant reductions in the incidence of acute otitis media were observed in any subgroups of children in whom oseltamivir treatment was started

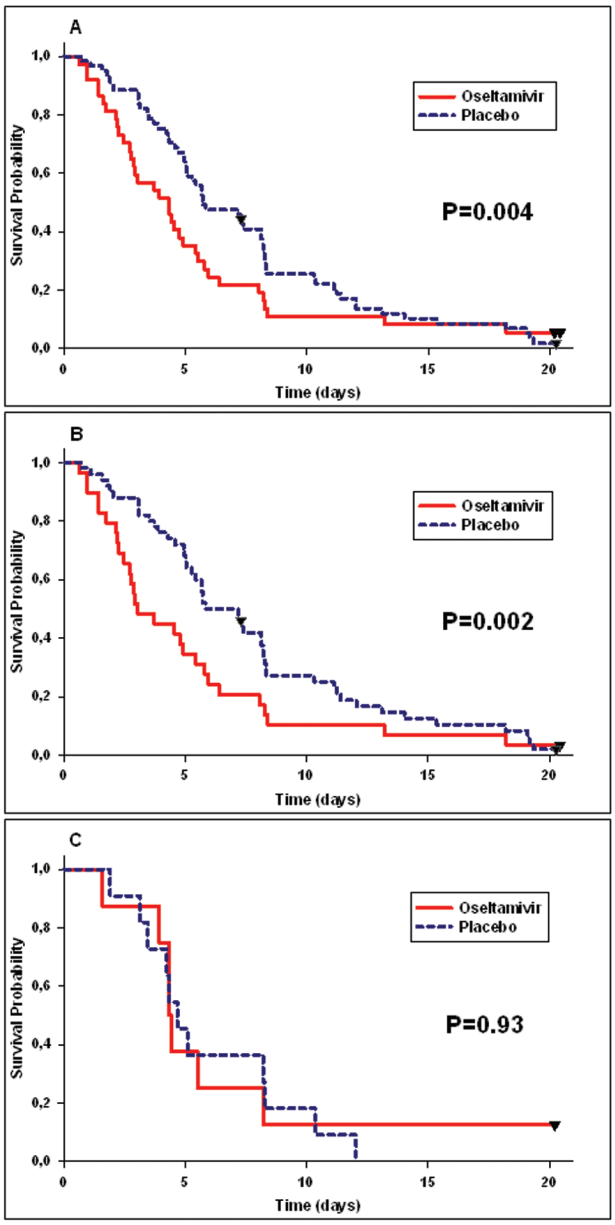

Figure 2. Time to resolution of illness in children with any influenza (*A*), influenza A (*B*), and influenza B (*C*) infections. The *black triangles* indicate censored data. *P* values for the differences between the groups were calculated with the Wilcoxon (survival) test.

within 24 hours of the onset of symptoms (Table 2). However, in the predefined subgroup of children with symptom onset within 12 hours, oseltamivir treatment decreased the incidence of development of acute otitis media by 85% (95% confidence interval [CI], 25%–97%; $P = .02$) in children with any influenza and by 79% (95% CI, −1% to 96%; $P = .08$) in children with influenza A.

Duration of illness. Oseltamivir treatment shortened the median time to resolution of illness by 1.4 days (4.3 vs 5.7; $P = .004$) in all children with any influenza and by 2.9 days (4.3 vs 7.3; $P = .009$) in unvaccinated children with any influenza (Table 3 and Figure 2). In children with influenza A infection, the median time to resolution of illness was reduced by 3.5 days (3.0 vs 6.5; $P = .002$) in all children and by 4.0 days (3.4 vs 7.3; $P = .006$) in unvaccinated children. No shortening of illness was demonstrated for children with influenza B infection (difference, 0.3 days; 4.4 vs 4.7; $P = .93$).

Absence from work and day care. Oseltamivir treatment reduced the median duration of parental absence from work by 2.0 days in children with any influenza and by 3.0 days in children with influenza A; children's absence from day care was reduced by 2.0 days in all of these groups (Table 3). No significant differences were observed in children with influenza B infection.

Other outcomes. In the oseltamivir group, the mean number of doses of antipyretics and/or analgesics was decreased by 1.5 (4.4 vs 5.9; $P = .03$) in children with any influenza and by 1.8 (4.3 vs 6.1; $P = .01$) in those with influenza A. No difference was observed in children with influenza B (4.8 vs 5.1; $P = .88$). None of the influenza-infected children was diagnosed with pneumonia or was hospitalized for any reason.

Safety and Tolerability

In the safety population of 406 children, 1 child receiving oseltamivir was hospitalized with bronchiolitis on day 3; no other serious adverse events were recorded in either group. Eleven (5.4%) of 202 children in the oseltamivir group and 5 (2.5%) of 204 children who were receiving placebo discontinued the treatment prematurely ($P = .12$; Figure 1).

Vomiting was reported as an adverse event in 59 (29.2%) children receiving oseltamivir and in 38 (18.6%) children receiving placebo ($P = .01$). The proportions of children with diarrhea were similar between the groups (oseltamivir, 35.1%, and placebo, 35.8%; $P = .89$). No significant differences were observed with respect to abdominal pain, exanthema, irritability, fatigue, headache, or decreased appetite between the groups. A total of 186 (92.1%) children receiving oseltamivir and 197 (96.6%) children receiving placebo were adherent to the study medication ($P = .05$).

DISCUSSION

Our results demonstrate that when started within 24 hours of the onset of influenza symptoms, the clinical efficacy of oseltamivir is substantially greater than what was estimated in a recent meta-analysis [16]. In children with influenza A, oseltamivir shortened the median time to resolution of illness from 6.5 to 3 days, a difference that most clinicians and parents may appreciate as being clinically significant. Furthermore, early os-

eltamivir treatment provided a 3-day reduction in parental absence from work among children with influenza A. The efficacy of oseltamivir was most pronounced among unvaccinated children, which was primarily because of the longer duration of symptoms in unvaccinated placebo recipients, compared with the duration of symptoms in vaccinated placebo recipients. Moreover, oseltamivir effectively prevented the development of acute otitis media as a complication of influenza when the treatment was started within 12 hours of symptom onset, but no efficacy could be demonstrated when the treatment was started within 24 hours.

Our findings are in accordance with a previous study among adults, in which early initiation of oseltamivir treatment was strongly associated with a shorter duration of influenza [17]. These findings are plausible with knowledge about the mechanism of action of oseltamivir and the pathogenesis of influenza. The efficacy of oseltamivir lies in its ability to prevent infection of new host cells by interfering with the release of progeny influenza viruses from infected cells [14]. Because the replication of influenza viruses peaks at 24–72 hours after the onset of symptoms and because the viral load correlates positively with the severity of symptoms [14, 22, 23], it could be expected that administering oseltamivir as early as possible after the onset of symptoms would provide the greatest clinical benefits.

In the only previous oseltamivir trial that included healthy children of the same age as in the present study, oseltamivir treatment started within 48 hours of symptom onset reduced the median duration of illness by 1.5 days in children 1–12 years of age and by ~1 day in a subgroup of children ≤2 years of age [10]. Our study was not designed to compare treatments started within 24 and 48 hours, and obviously our results are not directly comparable with those of Whitley and colleagues [10]. However, some cautious comparisons might be warranted on the basis that the time to resolution of illness was almost identically defined in both studies; the only difference was that our study included only infants and young children and defined a nonfebrile state as temperature ≤37.5°C, whereas the previous study included mostly older children and defined a nonfebrile state as temperature ≤37.2°C. Furthermore, in the placebo groups of both studies, the time to resolution of illness after enrollment was similar (5.7 days).

We did not observe any efficacy of oseltamivir in children with influenza B infections. Although the numbers of children with influenza B were too small for any firm conclusions, the finding is in agreement with recent reports on the reduced sensitivity of influenza B viruses to oseltamivir [24, 25]. The mean 50% inhibitory concentration values of oseltamivir for influenza B viruses are much higher than those for influenza A viruses, and some observational studies have shown the clinical efficacy of oseltamivir to be lower against influenza B infection than against influenza A infection, when measured by the duration of fever, mean viral titers during therapy, or duration of viral shedding [25–28].

Oseltamivir treatment effectively prevented the development of acute otitis media during influenza infection, but only when started within 12 hours of the onset of symptoms. The reasons for this finding are unclear. Viruses are known to play a key role in the initiation of the cascade of events that leads to development of acute otitis media [29, 30], and influenza viruses belong to the virus groups that most frequently predispose children to this complication [7–11, 31]. One potential explanation for the finding could be that influenza virus–induced inflammatory processes in the nasopharyngeal mucosa and in the Eustachian tube of infants and young children may be so intensive and may proceed so rapidly that, in terms of development of acute otitis media, they may reach the point of no return early in the course of influenza. Some support for this hypothesis can be derived from viral challenge studies in adult volunteers, in which the development of Eustachian tube dysfunction and negative middle ear pressure occurred more frequently during influenza A infections than during rhinovirus infections [32–34]. However, it is likely that many factors related to the pathogenesis of acute otitis media remain to be discovered. It should also be noted that the power of our study to demonstrate the presumed level of reduction of acute otitis media in children treated within 24 hours was limited, because the targeted number of influenza-infected children was not reached during the generally mild influenza seasons of this study.

Oseltamivir was well tolerated, which was shown by the high rate of adherence to the treatment. Vomiting was the sole adverse event reported more frequently in oseltamivir recipients than in those on placebo. Any other symptoms, including diarrhea, were equally common in both groups.

The difficulty of diagnosing influenza on clinical grounds alone may pose a challenge for the early use of oseltamivir in clinical practice. In our study that was performed during periods of confirmed local influenza activity, only 25% of acutely ill febrile infants and young children had influenza. This may be partially attributable to the extension of influenza vaccine recommendations in Finland in 2007 to include all children 6–35 months of age [35]. However, several studies in mostly unvaccinated populations have demonstrated that only a minority of influenza-like illnesses in unselected young children actually are caused by influenza viruses [6, 36–38]. Logistical issues, including access to health care, might also hamper the early initiation of treatment in some settings. Despite any practical problems, however, the great benefits afforded by early

administration of oseltamivir in young children clearly justify the efforts to overcome the hurdles.

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