USE OF THE SELECTIVE ORAL NEURAMINIDASE INHIBITOR OSELTAMIVIR TO PREVENT INFLUENZA

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ABSTRACT

Background Safe and effective antiviral agents are needed to prevent infection with influenza A and B viruses. Oseltamivir (GS4104), which can be administered orally, is the prodrug of GS4071, a potent and selective inhibitor of influenzavirus neuraminidases. We studied the use of oseltamivir for long-term prophylaxis against influenza in two placebo-controlled, double-blind trials at different U.S. sites during the winter of 1997–1998.

Methods We randomly assigned 1559 healthy, non-immunized adults 18 to 65 years old to receive either oral oseltamivir (75 mg given once or twice daily, for a total daily dose of 75 or 150 mg) or placebo for six weeks during a peak period of local influenzavirus activity. The primary end point with respect to efficacy was laboratory-confirmed influenza-like illness (defined as a temperature of at least 37.2°C accompanied by at least one respiratory and at least one systemic symptom).

Results In the two studies combined, the risk of influenza among subjects assigned to either once-daily or twice-daily oseltamivir (1.2 percent and 1.3 percent, respectively) was lower than that among subjects assigned to placebo (4.8 percent; $P<0.001$ and $P=0.001$ for the comparison with once-daily and twice-daily oseltamivir, respectively). The protective efficacy of oseltamivir in the two active-treatment groups combined was 74 percent (95 percent confidence interval, 53 to 88 percent) at all the sites combined and 82 percent (95 percent confidence interval, 60 to 93 percent) at sites in Virginia, where the rate of influenza infection was higher than the overall rate. For culture-proved influenza, the rate of protective efficacy in the two oseltamivir groups combined was 87 percent (95 percent confidence interval, 65 to 96 percent). The rate of laboratory-confirmed influenza infection was lower with oseltamivir than with placebo (5.3 percent vs. 10.6 percent, $P<0.001$). Oseltamivir was well tolerated but was associated with a greater frequency of nausea (12.1 percent and 14.6 percent in the once-daily and twice-daily groups, respectively) and vomiting (2.5 percent and 2.7 percent, respectively) than was placebo (nausea, 7.1 percent; vomiting, 0.8 percent). However, the frequency of premature discontinuation of drug or placebo was similar among the three groups (3.1 to 4.0 percent).

Conclusions Oseltamivir administered daily for six weeks by the oral route is safe and effective for the prevention of influenza. (N Engl J Med 1999;341: 1336-43.)

YEARLY immunization with inactivated vaccines is the main strategy for the prevention of influenza.[1] When substantial antigenic drift occurs after the formulation of a vaccine — as happened, for instance, during the 1997–1998 season, when the A/Sydney/5/97 variant of the H3N2 subtype circulated — large outbreaks may occur, particularly among institutionalized patients at high risk for infection.[2] Influenza B virus may also cause such outbreaks.[3,4] The recent cluster of human cases of H5N1-subtype influenza in Hong Kong is another reminder of the continuing threat of pandemic influenza.[5-7] In the event of the rapid spread of a new influenzavirus, antiviral agents could play a major part in protecting persons at high risk or even the general community while specific vaccines were being developed.[8,9] Prophylactic administration of amantadine or rimantadine, the currently approved anti-influenza drugs, can prevent symptomatic illness due to influenza A virus,[10] including strains that cause pandemic illness.[8] However, these agents are ineffective against influenza B virus, and their use is limited by adverse events (particularly in the case of amantadine)[10-12] and by the emergence and transmission of drug-resistant variants of the virus.[13]

Inhibitors of influenza neuraminidase are a new class of anti-influenza agents that potently and selectively reduce the replication of influenza A and B viruses.[14-16] Oseltamivir phosphate (GS4104, Tamiflu, Roche Laboratories, Nutley, N.J.), the orally bioavailable ethyl ester prodrug of the neuraminidase inhibitor GS4071 ([3R,4R,5S]-4-acetamido-5-amino-3-[1-ethylpropoxy]-1-cyclohexane-1-carboxylic acid]), is protective against experimentally induced influenza in animals and humans.[16-19] Oral administration of oseltamivir is safe and generally well tolerated in healthy persons at doses of up to 1000 mg per day,[20] and doses of 75 or 150 mg given twice daily are effective in treating acute influenza in adults.[21,22] We

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conducted two studies of oral oseltamivir for long-term prophylaxis against naturally occurring influenzavirus infection and associated illness.

METHODS

Study Design

Two identically designed, multicenter studies were performed over a six-week period. Both studies were parallel-group, randomized, placebo-controlled, double-blind trials. One trial was conducted at three centers in Virginia (Charlottesville, Norfolk, and Fairfax), and the other was conducted at two centers in Texas (Houston and Galveston) and one in Kansas (Kansas City) during the winter of 1997–1998.

Subjects

Healthy volunteers 18 to 65 years old were recruited by advertisement and were compensated for participation in the studies. Subjects were excluded if they had undergone influenza vaccination during the previous year or if they met one or more of the criteria for influenza immunization according to current guidelines.[1] Subjects who had an acute respiratory illness with fever during the week before drug administration was scheduled to begin were also excluded. Women of childbearing age were eligible if they were using adequate contraception regularly or if they were not sexually active. Subjects were allowed to take acetaminophen during the trial for the treatment of fever or discomfort. Written informed consent was obtained from each subject. The trial protocol and amendments were reviewed and approved by the appropriate ethics committee or institutional review board at each study site.

Study Protocol

Eight to 12 weeks before the anticipated start of the peak influenza season, subjects were screened by physical examination and laboratory tests (complete blood count, blood chemical analysis, and urinalysis) to determine their eligibility for participation. When there was a local increase in influenzavirus activity and an associated increase in the number of clinic visits for febrile respiratory illness, subjects returned to the study center to begin drug administration.

Subjects were assigned to receive one of two doses of oral oseltamivir (75 mg in capsule form given either once or twice daily, for a total daily dose of 75 or 150 mg) or placebo for six weeks. The study treatment was assigned on the basis of computer-generated random numbers, which were used for double-blind labeling. Before the first dose of the study drug was administered, blood samples were obtained for serum influenza hemagglutination-inhibition antibody tests and laboratory tests of safety, and urine samples were obtained for pregnancy tests. Subjects used daily diary cards to record their oral temperature, any medications taken, times of drug administration, and the presence or absence of seven key influenza symptoms (chills or sweats, aches, fatigue, headache, cough, sore throat, and nasal congestion).

Return visits were scheduled for week 3, week 6 (within 3 days after the final dose of study medication had been taken), and week 8 (or 10 to 14 days after the final dose). Subjects were also instructed to return to the clinic if fever or other symptoms of influenza developed; at these visits, nasal and pharyngeal swabs were collected for influenzavirus culture. Blood samples were obtained for influenza hemagglutination-inhibition antibody testing at the week 8 visit. Laboratory safety studies were repeated during the visits at week 3 and week 6.

Laboratory Procedures

For isolation of virus, combined anterior nasal and posterior pharyngeal swabs were placed in 3 ml of viral transport medium and shipped to a central laboratory for freezing at −70°C. Aliquots were subsequently thawed and inoculated onto monolayers of primary rhesus-monkey kidney cells (at Viromed Laboratories, Minneapolis). Viral recovery was monitored for seven days by hemagglutination with turkey erythrocytes, and isolates were subtyped by hemagglutination inhibition, with ferret antiserum as a reference. Hemagglutination-inhibition antibody testing was performed on paired serum specimens by standard techniques with use of antigens from influenzavirus strains known to be circulating during the 1997–1998 winter season: these strains were A/Texas/36/91 (H1N1), A/Wuhan/359/95 (H3N2), A/Sydney/5/97 (H3N2), and B/Harbin/7/94. The susceptibility of selected isolates to GS4071 was determined with use of a neuraminidase-inhibition assay performed as described elsewhere, with concentrations of substrate increased by a factor of four.[23]

Efficacy End Points

The primary end point with respect to efficacy was the incidence of laboratory-confirmed influenza-like illness during the six-week period of drug administration. Laboratory confirmation was defined as culture of influenzavirus within two days after the onset of influenza symptoms, an antibody titer on hemagglutination-inhibition testing that was at least four times as high as the base-line titer, or both. Influenza-like illness was defined clinically as an oral temperature of 37.2°C or higher, accompanied by at least one respiratory symptom (cough, sore throat, or nasal congestion) and at least one constitutional symptom (aches, fatigue, headache, or chills or sweats) occurring on the same day.

Other outcomes of interest were the incidences of culture-proved influenza-like illness during the six-week treatment period, laboratory-confirmed influenza-like illness associated with an oral temperature of 37.8°C or higher, laboratory-confirmed influenzavirus infection (symptomatic or asymptomatic), asymptomatic influenzavirus infection (defined as an antibody titer at least four times as high as the base-line titer in subjects without recorded symptoms), and influenza-like illness not associated with evidence (on culture or by laboratory testing) of influenzavirus infection.

Statistical Analysis

Intention-to-treat analysis was used to assess the results in the study population, which consisted of all subjects who were randomly assigned to a study group and who took at least one dose of the assigned study medication. The two active-treatment groups were compared with the placebo group with respect to the primary end point and other outcomes, which were analyzed with Fisher's exact test (with a bootstrap adjustment of P values to account for multiple testing in the case of the primary end point).[24] Protective efficacy was calculated as the rate of infection among subjects assigned to once-daily or twice-daily active drug divided by the illness rate among subjects assigned to placebo, with the result subtracted from 1 and expressed as a percentage. The method of Noether[25] was used to derive upper and lower bounds for the ratio of the illness rate in each active-drug group to the illness rate in the placebo group; these values were then subtracted from 100 to determine the upper and lower bounds of the confidence intervals for the estimates of protective efficacy. All analyses were performed with SAS software, version 6.12 (SAS Institute, Cary, N.C.).

The planned sample size for each study was 750 subjects (250 in each treatment group), on the assumptions that the incidence of laboratory-confirmed, symptomatic influenzavirus infection in the study sample would be 10 percent and that the protective efficacy of oral oseltamivir would be at least 70 percent. The overall incidence of laboratory-confirmed, symptomatic influenzavirus infection in the treatment groups in both studies combined was only 2.4 percent (38 of 1559 subjects). Therefore, before the investigators began the unblinded analysis, a decision was made to combine the data from the two studies and to complete the analysis for the combined study population.

RESULTS

Subjects

A total of 1562 subjects were enrolled. The demographic characteristics of the three treatment groups

in the combined studies were similar (Table 1). Women accounted for about 63 percent of the enrolled subjects, and the average age was approximately 35 years. Three subjects (two randomly assigned to receive placebo and one assigned to receive oseltamivir) were excluded from the analyses of safety and efficacy because they did not take any study medication. Only one subject (assigned to the placebo group) was ill at the time drug administration was to begin; this subject had culture-positive influenza, and this illness was excluded from the analysis of efficacy.

Similar numbers of subjects in the placebo and oseltamivir groups (3.1 to 4.0 percent) withdrew before completing the 6-week study; the median interval between the start of the treatment period and withdrawal was 21 to 23 days (Table 1). The most frequent reason for withdrawal in all three groups was adverse events or intercurrent illness, which occurred in similar proportions of subjects (1.3 to 1.9 percent) in each group. According to the number of returned capsules, the degree of compliance with the study-drug regimen was high and was similar among the three groups (Table 1). More than half the subjects in each group took all the prescribed doses of the study drug, and 90.6 to 92.7 percent took at least 90 percent of the doses.

Protective Efficacy

During the six-week treatment period, 38 subjects had episodes of laboratory-confirmed, influenza-like illness; 19 of the 38 had positive cultures. The proportion of subjects with laboratory-confirmed influenza-like illness was significantly lower in each of the oseltamivir groups (1.2 percent and 1.3 percent) than in the placebo group (4.8 percent) (Table 2). No significant differences in this respect were observed between the group assigned to once-daily oseltamivir and the group assigned to twice-daily oseltamivir. The efficacy of 75 mg of oral oseltamivir as prophylaxis against laboratory-confirmed, symptomatic influenza-like illness was 74 percent overall (95 percent confidence interval, 53 to 88 percent), 76 percent (95 percent confidence interval, 46 to 91 percent) when given once daily, and 72 percent (95 percent confidence interval, 40 to 89 percent) when given twice daily. At the three Virginia sites, where the rates of influenza were higher, the protective efficacy of 75 mg of oseltamivir was 82 percent overall (95 percent confidence interval, 60 to 93 percent), 84 percent (53 to 96 percent) in the once-daily group, and 79 percent (45 to 94 percent) in the twice-daily group. The frequency of influenza was very low in the placebo groups at the Texas and Kansas sites, and, consequently, there were no significant decreases in laboratory-confirmed influenza-like illness with either dose of oseltamivir.

All but two of the culture-proved infections (one case of influenza B in the placebo group and one case of influenza A/H1N1 in the twice-daily oseltamivir group) were due to influenza A virus (H3N2 subtype), predominately the A/Sydney/5/97 strain. In the placebo group, the number of cases was low ini-

TABLE 1. CHARACTERISTICS OF SUBJECTS ASSIGNED TO RECEIVE 75 mg OF ORAL OSELTAMIVIR ONCE OR TWICE DAILY OR PLACEBO FOR SIX WEEKS.

CHARACTERISTIC	OSELTAMIVIR		PLACEBO
	ONCE DAILY	TWICE DAILY	
No. of subjects			
All sites	520	520	519
Virginia	268	267	268
Texas and Kansas	252	253	251
Age — yr			
Mean	34.4	34.3	35.0
Range	18–65	18–63	18–64
Female sex — % of subjects	61	64	64
Premature withdrawal — no. of subjects (%)	17 (3.3)	16 (3.1)	21 (4.0)
Intercurrent illness or adverse event	8	7	10
Failure to return	5	6	4
Refusal of treatment	2	3	6
Other reasons	2	0	1
Level of compliance — no. of subjects (%)*			
100%	279 (53.7)	277 (53.3)	276 (53.2)
90–99%	198 (38.1)	205 (39.4)	194 (37.4)
80–89%	24 (4.6)	23 (4.4)	29 (5.6)
70–79%	7 (1.3)	3 (0.6)	5 (1.0)
<70%	12 (2.3)	12 (2.3)	15 (2.9)

*Level of compliance is expressed as the percentage of prescribed doses that were taken, according to the number of returned capsules.

tially, then increased and reached a plateau, and finally diminished again (Fig. 1). This pattern reflected the fact that the study drug was administered during the peak period of influenza activity in these communities. The number of cases of infection in the oseltamivir groups was low throughout the six-week period. In seven of the subjects (two assigned to receive placebo, one assigned to receive oseltamivir once daily, and four assigned to receive oseltamivir twice daily) laboratory-confirmed influenza developed after the completion of the six-week course of drug administration and before the final clinic visit during week 8. Among the patients assigned to receive oseltamivir, the illness occurred 1, 4, 10, 10, and 12 days after the completion of drug administration. Because of the low frequency of events, the duration of protection after cessation of the study drug could not be determined.

The proportion of subjects with culture-proved influenza, in whom illness was directly linked with active replication of virus, was also significantly lower in the oseltamivir groups combined (0.4 percent) than in the placebo group (2.9 percent) (Table 3). The efficacy of oral oseltamivir as prophylaxis against culture-positive influenza was 87 percent (95 percent confidence interval, 65 to 96 percent) in the oseltamivir groups combined, 100 percent in the group assigned to once-daily oseltamivir (the 95 percent confidence interval could not be estimated), and 73 percent in the twice-daily group (95 percent confidence interval, 29 to 93 percent). When two viral isolates from breakthrough illnesses in two subjects in the twice-daily oseltamivir group were examined in vitro, neither possessed neuraminidase enzymes with reduced susceptibility to GS4071 (50 percent inhibitory concentrations of 2.2 and 1.9 nmol per liter), when compared with the susceptibilities of more than 200 H3N2-subtype viruses circulating during the same season (mean 50 percent inhibitory concentration, 1.3 nmol per liter; range, 0.1 to 4.3). In addition, the incidence of laboratory-confirmed influenza with a temperature of 37.8°C or higher and of any influenzavirus infection, whether symptomatic or asymptomatic, was lower in subjects taking oseltamivir than in those taking placebo (Table 3). The efficacy of oseltamivir as prophylaxis against any laboratory-confirmed, symptomatic or asymptomatic influenzavirus infection was 50 percent overall and did not differ substantially between the once-daily and twice-daily oseltamivir groups.

There were no significant differences between either oseltamivir group and the placebo group in the proportions of subjects with serologically documented asymptomatic infection (2.5 percent of the subjects assigned to receive once-daily oseltamivir, 2.3 percent of those assigned to receive twice-daily oseltamivir, and 3.7 percent of those assigned to receive placebo), laboratory evidence of infection and symptoms that were inconsistent with the definition of clinical influenza-like illness (1.7 percent of the subjects assigned to receive once-daily oseltamivir, 1.5

TABLE 2. INCIDENCE OF LABORATORY-CONFIRMED INFLUENZA-LIKE ILLNESS IN THE OSELTAMIVIR AND PLACEBO GROUPS.*

VARIABLE	OSELTAMIVIR			PLACEBO
	ONCE DAILY	TWICE DAILY	COMBINED GROUPS	
All sites				
No. of subjects	520	520	1040	519
Laboratory-confirmed clinical influenza — no. of subjects (%)	6 (1.2)	7 (1.3)	13 (1.3)	25 (4.8)
Protective efficacy — % (95% CI)	76 (46 to 91)	72 (40 to 89)	74 (53 to 88)	
P value	<0.001	0.001	<0.001	
Virginia				
No. of subjects	268	267	535	268
Laboratory-confirmed clinical influenza — no. of subjects (%)	3 (1.1)	4 (1.5)	7 (1.3)	19 (7.1)
Protective efficacy — % (95% CI)	84 (53 to 96)	79 (45 to 94)	82 (60 to 93)	
P value	0.004	0.006	<0.001	
Texas and Kansas				
No. of subjects	252	253	505	251
Laboratory-confirmed clinical influenza — no. of subjects (%)	3 (1.2)	3 (1.2)	6 (1.2)	6 (2.4)
Protective efficacy — % (95% CI)	50 (−55 to 94)	50 (−54 to 94)	50 (−23 to 93)	
P value	0.49	0.47	0.39	

*Protective efficacy was estimated as the rate of laboratory-confirmed influenza-like illness among subjects assigned to once-daily or twice-daily active drug, divided by the rate among subjects assigned to placebo; the result was subtracted from 1 and expressed as a percentage. P values are for the comparison with the placebo group and were calculated with Fisher's exact test (adjusted by the bootstrap method for the primary end point). CI denotes confidence interval.

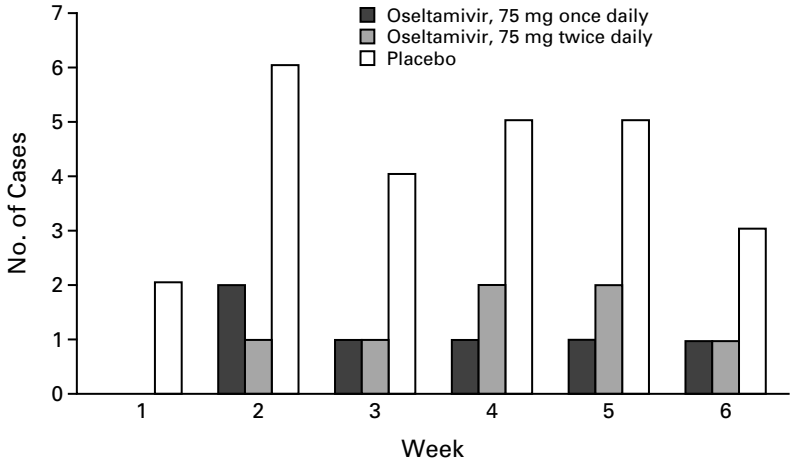

Figure 1. Incidence of Laboratory-Confirmed Influenza-Like Illness among Subjects Receiving 75 mg of Oseltamivir Once or Twice Daily (Total Daily Dose, 75 or 150 mg) or Placebo.

The number of subjects with laboratory-confirmed influenza-like illness during each week of the treatment period was lower in both oseltamivir groups than in the placebo group. At one week, none of the subjects in either oseltamivir group had influenza.

TABLE 3. INCIDENCE OF INFLUENZA AND INFLUENZA-LIKE ILLNESS IN THE OSELTAMIVIR AND PLACEBO GROUPS.*

INFECTION OR ILLNESS	OSELTAMIVIR			PLACEBO (N=519)
	ONCE DAILY (N=520)	TWICE DAILY (N=520)	COMBINED GROUPS (N=1040)	
Culture-proved influenza-like illness — no. of subjects (%)	0	4 (0.8)	4 (0.4)	15 (2.9)
Protective efficacy — % (95% CI)	100†	73 (29 to 93)	87 (65 to 96)	
P value	<0.001	0.011	<0.001	
Laboratory-confirmed influenza with fever ≥37.8°C — no. of subjects (%)	2 (0.4)	5 (1.0)	7 (0.7)	19 (3.7)
Protective efficacy — % (95% CI)	90 (61 to 98)	74 (37 to 91)	82 (60 to 93)	
P value	<0.001	0.004	<0.001	
Laboratory-confirmed infection (symptomatic or asymptomatic) — no. of subjects (%)	28 (5.4)	27 (5.2)	55 (5.3)	55 (10.6)
Protective efficacy — % (95% CI)	49 (24 to 69)	51 (26 to 70)	50 (31 to 67)	
P value	0.002	0.001	<0.001	
Influenza-like illness without laboratory evidence of infection — no. of subjects (%)	5 (1.0)	6 (1.2)	11 (1.1)	7 (1.3)
Protective efficacy — % (95% CI)	29 (−83 to 87)	15 (−108 to 84)	22 (−67 to 83)	
P value	0.58	0.79		

*P values are for the comparison with placebo. CI denotes confidence interval.

†The 95 percent confidence interval could not be estimated.

percent of those assigned to receive twice-daily oseltamivir, and 2.1 percent of those assigned to receive placebo), or influenza-like illness not attributed to influenzavirus on the basis of culture or hemagglutination-inhibition antibody testing (Table 3).

Adverse Effects

Oseltamivir was generally well tolerated and was not associated with laboratory-documented changes (data not shown). A total of 10 subjects (1.9 percent) withdrew from the study because of adverse events or intercurrent illness in the placebo group, as compared with 8 (1.5 percent) and 7 (1.3 percent) in the once-daily and twice-daily oseltamivir groups, respectively (Table 1). Two subjects (one assigned to receive placebo and one assigned to receive oseltamivir) were withdrawn because of transient increases in aminotransferase values. During the six weeks of drug

administration, the proportions of subjects who reported possible adverse events were similar among the study groups (74 to 80 percent). The most commonly reported adverse event was headache, which occurred in similar proportions of subjects in the three groups (39 to 47 percent).

Upper gastrointestinal disturbances, specifically nausea, occurred more frequently among subjects assigned to receive oseltamivir (12.1 percent in the once-daily group and 14.6 percent in the twice-daily group) than among those assigned to receive placebo (7.1 percent) (percentage-point differences, 5.0 in comparison with once-daily oseltamivir [95 percent confidence interval, 1.4 to 8.6 percentage points] and 7.5 in comparison with twice-daily oseltamivir [95 percent confidence interval, 3.7 to 11.2 percentage points]). Vomiting was reported by 2.5 and 2.7 percent of subjects in the once-daily and twice-daily oseltamivir groups, respectively, as compared with 0.8 percent of subjects in the placebo group (percentage-point differences, 1.7 in comparison with once-daily oseltamivir [95 percent confidence interval, 0.2 to 3.3 percentage points] and 1.9 in comparison with twice-daily oseltamivir [95 percent confidence interval, 0.3 to 3.5 percentage points]).

Only six subjects (0.6 percent of the oseltamivir groups combined) discontinued treatment because of adverse gastrointestinal events (three in the once-daily group and three in the twice-daily group). Most of the gastrointestinal events occurred during the first two days of the treatment period, and thereafter the frequency in the active-treatment groups declined to levels similar to those in the placebo group. The total proportion of treatment days on which there were gastrointestinal events was low in all the groups: nausea, 0.9, 1.5, and 0.4 percent of treatment days in the once-daily oseltamivir group, twice-daily oseltamivir group, and placebo group, respectively; vomiting, 0.06, 0.08, and 0.02 percent of treatment days, respectively.

DISCUSSION

Our findings demonstrate that oral oseltamivir is effective in preventing naturally occurring influenza and that it is well tolerated during long-term administration. Although the rates of influenza in our study populations were low and variable, there were significant overall reductions in laboratory-confirmed influenza-like illness (74 percent protective efficacy) and culture-proved influenza (87 percent efficacy) among the subjects assigned to oseltamivir given once or twice daily. The antiviral effect of oral oseltamivir was also reflected by the 50 percent decrease in the proportion of subjects with laboratory-confirmed, symptomatic or asymptomatic influenza. Once-daily administration of oseltamivir provided protection against infection and illness, a finding that is consistent with the prolonged plasma elimination half-life of the parent compound, GS4071.[20] In the Virginia cohort, the protective efficacy of once-daily administration was 84 percent, and no culture-proved illnesses occurred in any subjects assigned to this regimen. Once-daily administration also has the advantages of convenience for patients and possibly improved compliance and tolerance.

These findings confirm the results of studies of experimentally induced influenza in humans, in which 100 mg of oral oseltamivir taken once daily was highly protective against recovery of virus and against infection-associated illness.[19] Another neuraminidase inhibitor, zanamivir (GG167), has been found to have prophylactic activity against experimentally induced influenza in humans when administered intranasally[26] and against naturally occurring influenza when administered by inhalation once daily.[27] Inhaled zanamivir provided 67 percent protection against influenza-associated illness and 32 percent protection against infection during a four-week trial of prophylaxis in young adults.[27] Because of its limited oral bioavailability, zanamivir has been administered primarily by inhalation in field trials. This route of administration makes it difficult for many patients, such as young children or infirm elderly persons, to use the drug, and it probably does not result in effective levels of drug in the nasal passages, a limitation that may influence the degree of protection. A direct comparative study of oral oseltamivir and inhaled zanamivir would be necessary to answer this question.

Our study of prophylaxis was conducted in a population of young-to-middle-aged adults. The levels of protection against illness in our study are generally similar to those reported in similar populations with the use of either inactivated influenza vaccine, with a good match between the epidemic strain and the vaccine antigen, or oral amantadine or rimantadine as prophylaxis.[10,28] As in studies of other antiviral agents,[10,27,28] we also observed that the efficacy of oral oseltamivir in protecting against influenza-associated illness was higher than that against influenza infection. This finding indicates that some persons who receive prophylaxis have subclinical, probably immunizing, infection. However, the proportion of such persons is relatively small, and it should be assumed that protection ceases once drug administration is stopped. When influenza is active in a community, one strategy to provide protection in the event of delayed immunization in target populations is to administer an antiviral agent prophylactically in conjunction with inactivated vaccine.[1]

In our study there were slightly higher rates of breakthrough episodes of culture-proved illness during the treatment period among the subjects assigned to take the drug twice daily than among those assigned to take it once daily. The reasons for these failures of prophylaxis are unclear. There was no evidence of new drug resistance, as assessed by neuraminidase susceptibility, in the two viral isolates available

for study from these episodes. These cases occurred sporadically during the six-week treatment period (Fig. 1). According to study records, the affected subjects complied with the dose regimen and did not have adverse gastrointestinal effects. However, we did not directly assess compliance by measuring blood or urine levels of the parent compound, GS4071.

Long-term administration of oral oseltamivir was safe, and the rate of adverse events associated with oseltamivir was not higher than the rate of events associated with placebo, except for the incidence of gastrointestinal disturbances, which were usually minor. Most of these adverse events occurred during the first week of drug administration and resolved despite continued use of the drug. The proportion of subjects who stopped taking the drug prematurely because of adverse gastrointestinal effects was less than 1 percent in each active-treatment group. In an earlier study involving experimentally infected volunteers, nausea and, less often, vomiting occurred most often in the fasting state and at doses of 200 mg once or twice daily.[19] Participants in our study were instructed to take the study drug with meals or snacks. This probably accounted for the low frequency of gastrointestinal disturbances and the very low proportion of treatment days on which gastrointestinal events occurred.

In summary, treatment with oral oseltamivir, given either once or twice daily for six weeks, was effective and safe for the prevention of influenza-associated illness. These results demonstrate that an oral neuraminidase inhibitor is effective for prophylaxis against influenza. Although long-term or seasonal antiviral chemoprophylaxis against viral illness is a strategy that has limited applicability during periods of interpandemic influenza, it may be useful if a vaccine is unavailable or ineffective or cannot be tolerated; as an adjunct to vaccination in persons at high risk; or in the event of a pandemic.[1,8] In addition, our findings warrant studies of the use of oral oseltamivir for short-term prophylaxis against influenza in other settings, such as institutions in which there have been outbreaks of influenza and households in which members have been exposed to the virus.

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APPENDIX

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