

Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza

A Randomized Controlled Trial

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INFLUENZA IS ESTIMATED TO BE RESPONSIBLE for from 13.8 to 16.0 million excess respiratory illnesses per year in the United States among individuals younger than age 20 years, and for 4.1 to 4.5 million excess illnesses in individuals aged 20 years and older.¹ The symptoms of this disease are debilitating, and a typical case of influenza is associated with approximately 5 to 6 days of restricted activity, 3 to 4 days of bed disability, and about 3 days lost from work or school.^{2,3} In addition, complications of acute influenza, including bronchitis and pneumonia, are common, with approximately 150 000 hospitalizations and 20 000 deaths from influenza-related complications yearly in the United States.⁴

Although an effective vaccine is available, current treatment options for influenza are limited. Amantadine

For editorial comment see p 1057.

Context Previous studies have shown oseltamivir, a neuraminidase inhibitor, to be effective in preventing influenza and treating experimental influenza.

Objective To evaluate the efficacy and safety of oseltamivir in the treatment of naturally acquired influenza infection.

Design Randomized, placebo-controlled, double-blind study conducted January through March 1998.

Setting Sixty primary care and university health centers throughout the United States.

Participants A total of 629 healthy nonimmunized adults aged 18 to 65 years with febrile respiratory illness of no more than 36 hours' duration with temperature of 38°C or more plus at least 1 respiratory symptom and 1 constitutional symptom.

Interventions Individuals were randomized to 1 of 3 treatment groups with identical appearing pills: oral oseltamivir phosphate, 75 mg twice daily (n = 211) or 150 mg (n = 209) twice daily, or placebo (n = 209).

Main Outcome Measures Duration and severity of illness in individuals infected with influenza.

Results Two individuals withdrew before receiving medication and were excluded from further analyses. A total of 374 individuals (59.6%) were infected with influenza. Their duration of illness was reduced by more than 30% with both oseltamivir, 75 mg twice daily (median, 71.5 hours; $P < .001$), and oseltamivir, 150 mg twice daily (median, 69.9 hours; $P = .006$), compared with placebo (median, 103.3 hours). Severity of illness was reduced by 38% (median score, 597 score-hours; $P < .001$) with oseltamivir, 75 mg twice daily, and by 35% (median score, 626 score-hours; $P < .001$) with oseltamivir, 150 mg twice daily, vs placebo (median score, 963 score-hours). Oseltamivir treatment reduced the duration of fever and oseltamivir recipients returned to usual activities 2 to 3 days earlier than placebo recipients ($P \leq .05$). Secondary complications such as bronchitis and sinusitis occurred in 15% of placebo recipients compared with 7% of combined oseltamivir recipients ($P = .03$). Among all 629 subjects, oseltamivir reduced illness duration (76.3 hours and 74.3 hours for 75 mg and 150 mg, respectively, vs 97.0 hours for placebo; $P = .004$ for both comparisons) and illness severity (686 score-hours and 629 score-hours for 75 mg and 150 mg, respectively, vs 887 score-hours for placebo; $P < .001$ for both comparisons). Nausea and vomiting occurred more frequently in both oseltamivir groups (combined, 18.0% and 14.1%, respectively; $P = .002$) than in the placebo group (7.4% and 3.4%; $P < .001$).

Conclusions Our data suggest that oral oseltamivir treatment reduces the duration and severity of acute influenza in healthy adults and may decrease the incidence of secondary complications.

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hydrochloride and rimantadine hydrochloride are effective for early treatment of influenza A, but have no activity against influenza B viruses and are associated with the emergence of resistant viruses in treated individuals.⁵ In addition, both drugs can cause central nervous system and gastrointestinal adverse effects, which may be more common in older individuals.⁶ The neuraminidase inhibitor zanamivir is also effective in the treatment of influenza.⁷⁻⁹ However, zanamivir must be administered topically (ie, by inhalation or intranasally) or parenterally¹⁰ to be effective.

Osetamivir carboxylate is a potent and specific influenza neuraminidase inhibitor¹¹ that inhibits replication of a wide variety of influenza A and B viruses in vitro.¹² Osetamivir phosphate (oseltamivir) is the ethyl ester prodrug of oseltamivir carboxylate, and oral administration of this agent results in sustained plasma levels of the active drug.¹³ Osetamivir was effective when administered orally in treatment of influenza A infection in animals¹² and experimentally infected humans¹⁴ and in prevention of influenza illness.¹⁵

We designed the current trial to test the hypothesis that early treatment with oseltamivir would be well tolerated and result in reductions in the severity and duration of acute naturally acquired influenza illness. The study was conducted to determine safety and clinical efficacy of 2 different doses of oseltamivir administered for 5 days beginning within 36 hours of symptom onset in adults with microbiologically proven influenza.

METHODS

This study was in full conformance with the principles of the Declaration of Helsinki.¹⁶ Institutional review boards from each participating center reviewed and approved the protocol and consent form prior to study start. All participants gave written informed consent prior to enrollment and were financially compensated for their participation.

Clinical Study Design

The study was conducted as a double-blind, stratified, randomized, placebo-controlled, multicenter trial conducted during the influenza epidemic season from January to March 1998 at 60 centers in the United States.

Participants

Previously healthy adults aged 18 to 65 years who presented within 36 hours of onset of influenza symptoms and who had documented oral temperature of 38°C or higher at enrollment plus 1 or more respiratory symptom (cough, sore throat, or nasal symptoms) and 1 or more constitutional symptom (headache, malaise, myalgia, sweats and/or chills, or fatigue) were enrolled. Women were required to have a negative urine pregnancy test before drug administration.

Individuals were excluded from the study if they had received influenza vaccination in the 12 months prior to the beginning of the study; had active, clinically significant chronic illness or human immunodeficiency virus disease; were receiving systemic steroids or other immunosuppressants; or had a history of alcohol or drug abuse.

Drug Administration

Participants were randomly assigned to 1 of 3 treatment groups: oseltamivir, 75 mg or 150 mg orally twice daily, or matching placebo for 5 days. Randomization occurred at the time of study entry by telephone contact with an automated service that had sole access to the code key and was stratified by study site and smoking behavior. Participants and staff remained blinded to allocation status throughout the study. Compliance was assessed by checking patient records of the date and time of each dose and verified by counting capsule returns for each patient.

Participants were instructed to use acetaminophen, provided on enrollment by study personnel, for symptom relief. The use of acetaminophen and any other medications for symptom relief was recorded on the case record form.

Clinical Monitoring

Participants recorded the severity of 7 influenza symptoms (cough, nasal obstruction, sore throat, fatigue, headache, myalgia, and feverishness) using a 4-point scale (0, absent; 3, severe) twice daily for 21 days. Oral temperature was also taken by the patient with a digital thermometer twice daily and recorded on the diary card. On each day during the dosing period, participants recorded their ability to perform usual activities on a diary card using an 11-point visual analog scale (unable to perform normal activity, 0; fully able to perform normal activity, 10). In addition, participants were asked to complete a visual analog scale of their opinion of overall health status on which they were requested to provide an assessment of their normal preinfluenza health on an 11-point scale (0, worst health and 10, best possible health). Following this, they were asked to record their assessment of health status at baseline and over a 24-hour period once daily in the evening. The use of these scales had been validated in a pilot study conducted among English-speaking volunteers during the influenza season in Australia in 1997. The scales were demonstrated to be easily comprehended by English-speaking volunteers and correlate well with other questions about activity and with influenza symptom scores (Influenza Questionnaire Pilot Study Report, August 1997, Hoffmann-La Roche, data on file).

Laboratory Methods

Anterior nose and posterior pharyngeal throat swabs for isolation of influenza virus were taken at baseline (day 0) and on days 1, 3, 5, and 7 of the study. Swabs were taken from both nostrils and the throat, placed into 3 mL of viral transport medium, and transported on wet ice to a central laboratory within 24 hours. At the central laboratory, the swab samples were eluted, divided into aliquots, and immediately frozen at -70°C. Initial virus isolation was performed in primary rhesus monkey kidney cells, and all samples for an individual were tested

in the same assay run. The presence of virus in the cell culture was determined by immunofluorescence, using a pool of antibodies specific for influenza A and B viruses. Type and subtype of the influenza viruses isolated were determined by hemagglutination inhibition assay (HAI) using specific antisera. The titer of virus in virus-positive samples was determined by serial dilution of a fresh aliquot in tertiary cynomolgus monkey kidney cells. Titers were calculated as \log_{10} tissue culture infective dose₅₀ (TCID₅₀)/mL of viral transport medium using the Spearman-Kärber equation.¹⁷ The last isolate recovered from each participant was tested for neuraminidase susceptibil-

ity to oseltamivir carboxylate by fluorometric substrate assay¹¹ (total of 175 samples tested).

Serum samples for HAI antibody titer were obtained at baseline and on day 21 after enrollment. The HAI assays were performed by standard methods using antigens known to be circulating during the 1997-1998 season (influenza A/Shenzhen/95 [H1N1], A/Wuhan/95 [H3N2], and A/Sydney/97 [H3N2], and B/Harbin/95).¹⁸ The definition of seroresponse was a 4-fold or greater rise in type-specific antibody between the baseline and day 21 samples. Primary virus isolation and serum HAI antibody testing were performed at Viromed Laboratories Inc, Minneapolis,

Minn, and virus titrations were performed at Erasmus University, Rotterdam, the Netherlands. All laboratory tests were performed by individuals blinded to study assignment.

Case Definition

For the primary efficacy analysis, laboratory-documented influenza infection was defined as isolation of influenza virus from nasal secretions and/or a 4-fold or greater HAI antibody response.

Efficacy End Points

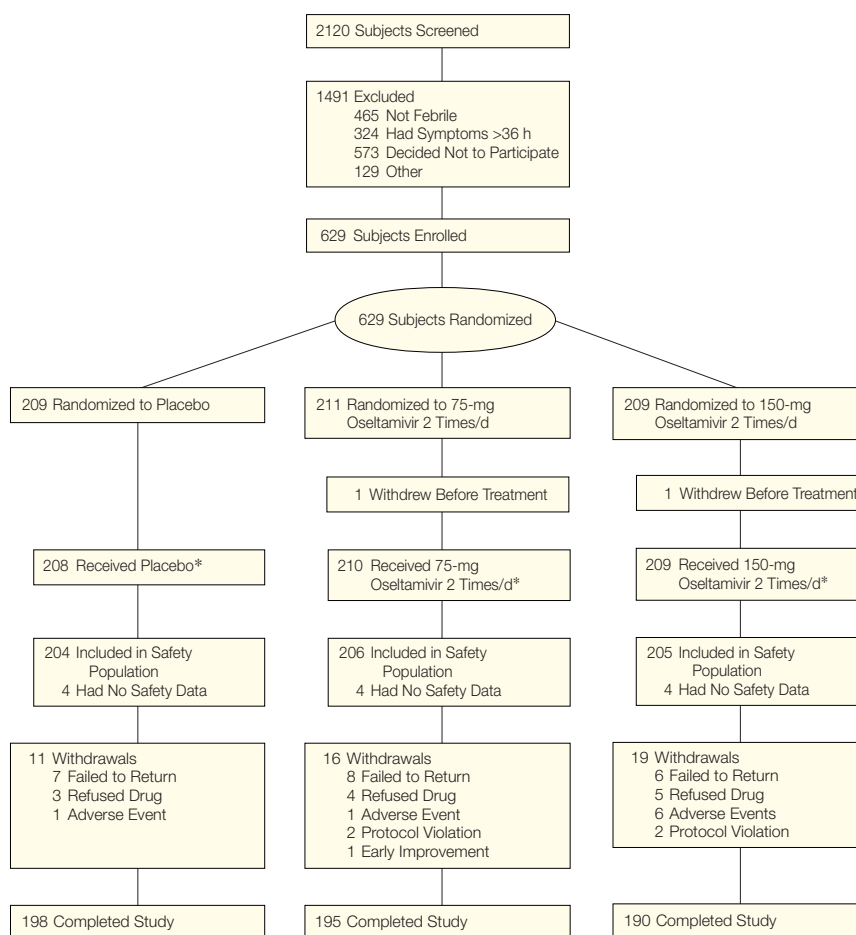
The primary efficacy end point was time to resolution of illness, defined as time from study drug initiation to time of alleviation of symptoms, among individuals with influenza infection. Symptom alleviation was considered to occur at the start of the first 24-hour period in which all influenza symptoms were scored 1 or less (mild or none) and remained so for 24 hours. The effect of treatment on the severity of illness was also assessed by an area under the curve (AUC) analysis of total symptom scores. For this analysis, the AUC was calculated as the product of the daily symptom score times the duration of illness, as defined above, and expressed as "score-hours." Other end points included duration and severity of individual symptoms; incidence of secondary complications of influenza such as otitis, bronchitis, sinusitis, and pneumonia; and quantity of viral shedding.

Quality-of-life measures included time to return to normal states of health and activity. Return to normal status was defined as the time (in hours) from study drug initiation to the first 24-hour period in which participants returned to their normal state and remained so for 24 hours.

Data Analysis

The primary efficacy analyses were carried out for participants who received at least 1 dose of study drug and had laboratory-confirmed influenza infection. A secondary efficacy analysis was also performed for all subjects who received study drug irrespective of labo-

Figure 1. Disposition of Study Participants



Asterisk indicates dispensing errors and participant crossover between groups in a total of 5 participants. See "Results" section.

ratory evidence of infection. For the primary end point, comparisons were performed using a weighted Mantel-Haenszel test stratified for region and smoking status. Investigation of the consistency of treatment effects between regions and smoking groups was performed. Subjects who withdrew before symptoms were alleviated were censored at the time of withdrawal.

For extent and severity of illness, the placebo group was compared with each active treatment group using an extended Wilcoxon rank sum test (van Elteren) stratified for region and smoking status. Duration of viral shedding and time to return to normal states of health and activity were compared between placebo and each active treatment group using a weighted Mantel-Haenszel test. Viral titers were assessed by the extended Wilcoxon rank sum test (van Elteren). Adjustments of *P* values for multiple comparisons of treatment groups were made for the primary end point, but not for other parameters. The within-group 95% confidence intervals (CIs) for medians were calculated using the method of Brookmeyer and Crowley.¹⁹

The safety population included all participants who received at least 1 dose of drug and for whom postbaseline safety data were available. Formal statistical hypothesis testing was not performed; 95% CIs for the difference in nausea and vomiting rates were calculated using a normal approximation.

Sample size calculations assumed an overall 2-sided 5% significance level to be distributed equally between the comparisons of 75 mg and 100 mg of oseltamivir, respectively, vs placebo. A sample size of 85 in each group was estimated to have at least 80% power to detect a difference of 1.5 days in time to alleviation of all symptoms, assuming a common SD of 3 days and a significance level of 0.025. Sample size calculations were performed using a normal approximation to the Wilcoxon rank sum test. All analyses were performed using SAS software, version 6.12 (SAS Institute, Cary, NC).

RESULTS

A total of 629 participants were recruited from 60 centers. The disposition of the participants in the trial is shown in FIGURE 1. Of the 629 individuals enrolled in the study, 209, 211, and 209 were randomized to receive placebo; oseltamivir, 75 mg; and oseltamivir, 150 mg, respectively. Two participants (1 in the 75-mg group and 1 in the 150-mg group) withdrew from the study after randomization but before the study drug was dispensed. In addition, a small number of participants did not receive treatment as randomized because of dispensing errors. One person randomized to receive placebo received 75 mg and 1 person, 150 mg of oseltamivir twice daily; 1 person randomized to oseltamivir, 75 mg twice daily, received placebo, and 1 received 150 mg of oseltamivir twice daily; and 1 person randomized to receive oseltamivir, 150 mg twice daily, received 75 mg twice daily. For purposes of efficacy analysis, participants were analyzed according to the group to which they were initially randomized excluding the 2 subjects who with-

drew before medication was dispensed; for purposes of the safety analysis, participants were analyzed according to the drug actually received. In addition, safety data were not available from 4 participants in each group and were therefore not included in the safety population. Of the 627 participants who received treatment 374 (59.6%) were influenza infected and included in the primary efficacy analysis. Of these, 343 (92%) had influenza A (H3N2) and 299 (80%) were culture positive. The demographic and clinical characteristics of the participants and the proportions infected with influenza virus in each group are described in TABLE 1. No important differences were observed among treatment groups. Median duration of illness prior to enrollment and average symptom score and mean temperature on enrollment were similar in all 3 infected treatment groups. Adherence to the assigned treatment regimen was excellent. Overall, 97% of placebo recipients, 98% of 75-mg oseltamivir recipients, and 95% of 150-mg oseltamivir recipients who completed the study took all 10 tablets as directed.

Table 1. Demographic Characteristics of the Safety Population and Clinical Characteristics of Influenza-Infected Participants

Characteristic	Study Groups		
	Placebo (n = 209)	Osetamivir, 75 mg (n = 210)	Osetamivir, 150 mg (n = 208)
	Individuals Receiving Medication		
Age, mean (SD), y	32.6 (10.2)	32.2 (10.8)	33.1 (9.8)
Men, No. (%)	97 (46)	98 (47)	114 (55)
Smokers, No. (%)	29 (14)	30 (14)	35 (17)
Infected, No. (%)*	129 (62)	124 (59)	121 (58)
Influenza A†	122	112	109
Influenza B	2	3	4
Unknown type‡	5	9	8
	Individuals Infected With Influenza		
Duration of illness before study, median (range), h	26 (2-39)	24 (0-41)	27 (2-37)
Symptom score at enrollment, mean (SD)§	14.6 (3.5)	14.0 (3.3)	13.9 (3.4)
Oral temperature, mean (SD), °C	38.3 (0.5)	38.3 (0.5)	38.3 (0.5)

*Among infected participants, 90 (70%) in the placebo group, 105 (85%) in the 75-mg group, and 104 (86%) in the 150-mg group had virus detected in nasopharyngeal secretions, while the remaining subjects were defined as infected on serologic grounds alone.

†Influenza A virus infections were predominantly H3N2; 1 infection in the 150-mg group was due to H1N1 virus.

‡These participants had isolation of viruses from nasopharyngeal secretions that were positive for influenza by immunofluorescence using pooled A and B reagents, but had insufficient growth for typing; virus could not be reisolated from the original clinical sample, and the type of infection could not be determined serologically.

§See "Clinical Monitoring" section for description of symptom scores.

Table 2. Duration and Severity of Illness and Proportion of Participants Resuming Usual Health and Activity*

	Influenza-Infected Participants			All Treated Participants		
	Placebo (n = 129)	Osetamivir, 75 mg (n = 124)	Osetamivir, 150 mg (n = 121)	Placebo (n = 209)	Osetamivir, 75 mg (n = 210)	Osetamivir, 150 mg (n = 208)
Illness duration, median (95% CI), h	103.3 (92.6-118.7)	71.5 (60.0-93.2)	69.9 (60.0-87.9)	97.0 (86.3-113.6)	76.3 (66.3-89.2)	74.3 (68.1-87.5)
<i>P</i> value†		<.001	.006		<.004	.004
Illness severity, median (range), score	963 (0-4360)	597 (60-2822)	626 (0-3079)	887 (0-5717)	686 (0-4604)	629 (0-4474)
<i>P</i> value‡		<.001	<.001		<.001	<.001
Return to normal health, median (95% CI), h§	178 (156-273)	132 (123-152)	154 (131-157)	178 (156-273)	134 (128-155)	155 (133-157)
<i>P</i> value		<.001	.03		<.001	.03
Return to normal activity, median (95% CI), h§	225 (175-276)	157 (151-198)	180 (154-221)	230 (179-277)	173 (155-203)	202 (176-231)
<i>P</i> value		.02	.05		.01	.10

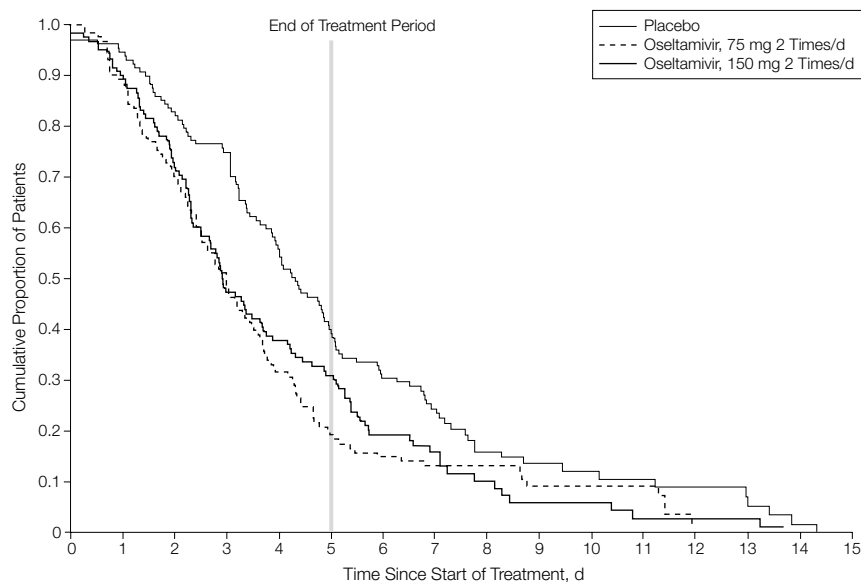
*CI indicates confidence interval. All *P* values are comparison vs placebo. See "Clinical Monitoring" section for a description of symptom scores.

†Determined by weighted Mantel-Haenszel test, adjusted for multiple comparisons.

‡Determined by extended Wilcoxon rank sum test.

§Within-group comparison.

||Determined by weighted Mantel-Haenszel test.

Figure 2. Time to Alleviation of All Symptoms in Influenza-Infected Patients

Participants with missing values were censored. One patient (not shown, osetamivir, 75-mg group) had a censored value of 20.3 days. $P < .001$ for placebo vs osetamivir, 75 mg twice daily; $P = .006$ for placebo vs osetamivir, 150 mg, twice daily.

Clinical Outcomes

The effect of osetamivir treatment on alleviation of illness is shown in TABLE 2. Both dose levels of osetamivir resulted in statistically significant reductions in the duration and severity of illness among those infected with influenza virus. The duration of illness, defined as the time to the beginning of

the first 24-hour period in which all influenza symptoms were rated as mild or less, was 103.3 hours (4.3 days) in the placebo group. In contrast, the duration of illness was reduced to 71.5 hours (3.0 days) in the 75-mg group, and to 69.9 hours (2.9 days) in the 150-mg group. Similarly, treatment with osetamivir at either 75 or 150 mg

twice daily resulted in statistically significant reductions ($P < .001$ and $P = .006$, respectively) in the symptom score AUC, reflecting both the severity and duration of illness. There were no differences between the 2 doses of osetamivir with regard to these effects. Overall, osetamivir treatment reduced median duration of illness by more than 30% ($P = .006$) and median severity of illness by approximately 40% ($P < .001$). Treatment benefit was apparent soon after administration, with individuals receiving osetamivir reporting alleviation of illness more frequently than those receiving placebo as early as 24 hours after the onset of treatment (FIGURE 2). In addition, individuals receiving osetamivir reported significantly more rapid return to normal overall health (24-46 hours faster) and resumption of usual activities (45-68 hours faster) (TABLE 2).

Duration and severity of each individual influenza symptom recorded in infected subjects were also reduced with osetamivir (TABLE 3). In particular, duration of cough was reduced from a median of 55 hours in the placebo group to 31 hours (43% reduction) in the 75-mg group, and 40 hours (27% reduction) in the 150-mg group. The duration of myalgias was also reduced, from a median of 28 hours in placebo recipients to 16 hours (42% reduc-

tion) in the 75-mg group, and 19 hours (32% reduction) in the 150-mg group.

The daily proportion of infected subjects reporting fever (oral temperature of $\geq 38^{\circ}\text{C}$) was reduced by treatment, and a reduction in fever was evident within 24 hours of therapy (FIGURE 3). The percentage of subjects with fever at 24 hours was 39% in the placebo group, compared with 26% in the 75-mg group (13% difference; 95% CI, 25%-2%) and 21% in the 150-mg group (18% difference; 95% CI, 29%-6%). The use of acetaminophen also was lower in individuals receiving oseltamivir (median, 4.0-4.5 g per patient) than in those receiving placebo (median, 5.5 g per patient).

Overall incidence of physician-diagnosed secondary complications (predefined as pneumonia, bronchitis, sinusitis, and otitis media) in those with influenza was reduced by 50% in individuals receiving oseltamivir vs those receiving placebo. A similar reduction was observed in the proportion of these individuals receiving antibiotics for influenza complications (TABLE 4).

Because it is likely that an antiviral drug to treat influenza would be used in the absence of a specific microbiologic diagnosis, we also performed an analysis of the effect of treatment on all individuals who received medication regardless of microbiologic results (Table 2). Oseltamivir also had a significant benefit in this analysis. Median time to alleviation of symptoms was reduced by 21% and 23% and severity of illness by 23% and 29% in recipients of 75 mg and 150 mg twice daily, respectively. In addition, recipients of oseltamivir returned to normal health and activities more rapidly than placebo recipients among the group as a whole. Complications of influenza occurred in 28 placebo recipients (13%), 18 recipients (9%) of 75-mg oseltamivir, and 13 recipients (6%) of 150-mg oseltamivir (combined oseltamivir results vs placebo for Fisher exact test, $P = .02$).

Virologic Outcomes

Analysis of the effect of oseltamivir on virus shedding was conducted on the subset of participants with a baseline sample

Table 3. Duration and Severity of Symptoms of Influenza-Infected Patients*

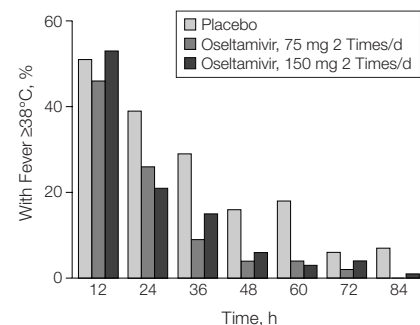
	Study Groups		
	Placebo (n = 129)	Oseltamivir, 75 mg (n = 124)	Oseltamivir, 150 mg (n = 121)
Cough			
Duration, h	55 (36-73)	31 (24-42)	40 (26-48)
Severity, score-hours	110 (0-844)	67 (0-400)	71 (0-459)
Myalgia			
Duration, h	28 (24-36)	16 (10-20)	19 (13-22)
Severity, score-hours	62 (0-288)	33 (0-369)	42 (0-359)
Nasal obstruction			
Duration, h	43 (31-64)	33 (25-43)	32 (24-46)
Severity, score-hours	80 (0-873)	60 (0-540)	57 (0-658)
Sore throat			
Duration, h	21 (8-29)	10 (4-19)	10 (0-18)
Severity, score-hours	29 (0-548)	20 (413)	16 (0-288)
Fatigue			
Duration, h	41 (26-50)	24 (19-34)	25 (19-32)
Severity, score-hours	89 (0-917)	54 (0-1178)	57 (0-319)
Headache			
Duration, h	14 (8-23)	8 (6-15)	10 (6-17)
Severity, score-hours	34 (0-278)	16 (0-611)	21 (0-336)
Feverishness			
Duration, h	23 (16-29)	10 (8-14)	8 (5-10)
Severity, score-hours	49 (0-314)	21 (0-232)	17 (0-194)

*"Score-hours" are the daily symptom score (see "Clinical Monitoring" section) times the duration of illness. Duration data are presented as median (95% confidence interval), and severity data as median (range).

positive for influenza and for whom appropriate samples were collected on days 1, 3, and 5 (TABLE 5). The median viral titer at enrollment was similar, and a rapid decline in virus shedding was observed in all 3 groups. After 24 hours of treatment, median viral titers had decreased by 1.2 logs in the placebo group vs 1.7 and 2.0 logs in the 75-mg and 150-mg oseltamivir groups, respectively, but these differences were not statistically significant. The proportions of participants shedding virus at each time point were similar in all 3 groups, and few participants in any group were shedding virus by 72 hours after initiation of therapy. There was no evidence of a rebound of virus shedding at drug discontinuation.

All isolates from the last day of virus shedding were tested for drug susceptibility, and a virus with altered neuraminidase susceptibility to oseltamivir carboxylate was detected in 1 recipient of 75-mg oseltamivir on day 3 of treatment. The 50% neuraminidase inhibitory concentration for oseltamivir carboxylate for the pretreatment isolate from the subject was 0.93 nmol/L, while the posttreatment 50% neuraminidase inhibitory concen-

Figure 3. Proportion of Subjects Reporting Fever at Each 12-Hour Interval During Study



tration was 6814 nmol/L. Sequence data from this virus are not yet available. The individual from whom resistant virus was isolated was a 49-year-old female smoker who was enrolled 20 hours after onset of symptoms. She complained of moderate cough for 8 days, so that the duration of illness in this individual was 8 days. None of her symptoms became worse after cessation of therapy, and she did not experience an influenza complication. Virus was not isolated from this individual on days 5 or 7.

Proportions of participants with 4-fold or greater rises in HAI antibody were comparable among treatment groups (data not shown). Similarly, there were no differences among treatment groups for the geometric mean HAI antibody rise from baseline to convalescence (mean, 16.1-fold, 15.9-fold, and 15.7-fold rise in those receiving placebo and oseltamivir, 75 mg and 150 mg, respectively).

Safety Analysis

Oral oseltamivir was well tolerated. No changes occurred in standard laboratory safety evaluations in any treatment groups (data not shown) and there were no drug-related serious adverse events. Upper gastrointestinal effects (nausea or nausea with vomit-

ing) were reported more frequently in those receiving oseltamivir. For nausea, these rates were 7.4% (15/204) for placebo recipients, 17% (35/206) for recipients of 75-mg oseltamivir and 19% (39/205) for recipients of 150-mg oseltamivir (for overall difference in the 3 groups, $P = .002$; for differences between placebo and 75-mg and 150-mg oseltamivir, $P = .002$ and $P < .001$, respectively). For vomiting, the rates were 3.4% (7/204) with placebo, 13.1% (27/206) with 75-mg oseltamivir, and 15.1% (31/205) with 150-mg oseltamivir ($P < .001$ for overall difference in the 3 groups and differences between placebo and 75-mg and 150-mg oseltamivir). Despite mild gastrointestinal intolerance, the number of participants withdrawing from the study during

therapy was low (3% in the placebo group, 1.5% in the 75-mg group, and 2% in 150-mg group), and only 1 participant (oseltamivir, 150-mg group) withdrew prematurely because of gastrointestinal events.

COMMENT

The results of this study indicate that the oral neuraminidase inhibitor oseltamivir is an effective treatment for acute influenza in adults. Treatment within 36 hours of symptom onset resulted in approximately 30% reduction in illness duration, approximately 40% in illness severity, and by more than 2 days in the time to resumption of usual activities vs placebo. Treatment with oseltamivir resulted in reductions in fever and duration and severity of individual influenza symptoms, including cough and myalgia, 2 of the more disabling symptoms. A parallel trial conducted in Canada and Europe during the same influenza season found similar benefits with oseltamivir treatment.²⁰ These outcomes represent a clinically significant reduction in overall disease burden with oseltamivir treatment.

Complications of influenza, such as bacterial superinfections, pneumonia, and hospitalization, are common in individuals with certain chronic medical conditions.^{21,22} Less severe complications, such as bronchitis and sinusitis in healthy adults and otitis media in children, have been reported at rates between 1% and 30% in various studies.²³ In the current study, the frequency of secondary complications of influenza and associated antibiotic use for presumed bacterial complications were significantly reduced in oseltamivir-treated subjects. These results are similar to those reported with zanamivir in studies conducted in healthy adults or those with mild asthma.^{8,24} While no formalized criteria were used to define bronchitis, pneumonia, or sinusitis, the functional definitions used in this study probably reflect actual medical practice. Our findings raise the possibility that early treatment of influenza with an effective antiviral drug

Table 4. Number of Influenza-Infected Patients Experiencing Secondary Complications as a Result of Influenza Illness and Antibiotic Use Over the Treatment Period

Complication	Study Group, No.		
	Placebo (n = 129)	Oseltamivir, 75 mg (n = 124)	Oseltamivir, 150 mg (n = 121)
Otitis media	1	0	0
Sinusitis	11	6	4
Bronchitis	8	5	2
Pneumonia	1	0	0
Any secondary complication (%)	19 (15)	11 (9)*	6 (5)*
Antibiotic use (%)	14 (11)	8 (6)†	4 (3)†

*Combined oseltamivir results vs placebo (Fisher exact test), $P = .03$.

†Combined oseltamivir results vs placebo (Fisher exact test), $P = .05$.

Table 5. Participants' Viral Titers*

	Study Group		
	Placebo (n = 71)	Oseltamivir, 75 mg (n = 67)	Oseltamivir, 150 mg (n = 73)
Baseline			
No. (%) shedding virus	71 (100)	67 (100)	73 (100)
Median titer (range)	3.5 (0.5-6.5)	3.5 (0.5-6.0)	3.3 (0.5-6.0)
Day 1			
No. (%) shedding virus	60 (85)	58 (87)	57 (78)
Median titer (range)	2.3 (0.0-5.5)	1.8 (0.0-6.0)	1.3 (0.0-5.3)
Day 3			
No. (%) shedding virus	20 (28)	19 (28)	20 (27)
Median titer (range)	0.0 (0.0-5.0)	0.0 (0.0-4.0)	0.0 (0.0-3.5)
Day 5			
No. (%) shedding virus	3 (4)	1 (1)	4 (5)
Median titer (range)	0.0 (0.0-2.3)	0.0 (0.0-0.5)	0.0 (0.0-0.5)
Day 7			
No. (%) shedding virus	0 (0)	0 (0)	0 (0)
Median titer (range)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)

*Subset of individuals with a baseline sample positive for influenza and who had samples collected at all time points. Viral titers measured as log₁₀ tissue culture infective dose₅₀ (TCID₅₀)/mL.

might reduce the frequency of complications in high-risk populations and potentially reduce hospitalization rates.

Lost time from work or school and reductions in performance represent important effects of influenza on healthy adults.^{25,26} While our study was not specifically designed to evaluate the economic benefit of antiviral therapy, it is notable that the reduced levels of influenza symptoms in treated subjects were accompanied by a significantly more rapid return to normal activities, which may provide another rationale for early use of antiviral treatment for influenza in previously healthy adults.

Comparisons of our study results with those of other antiviral approaches to acute influenza are complicated both by differences between trials in the specific outcome measurements and by the variable nature of influenza illness each year. However, the levels of reductions in symptoms seen in this study are broadly comparable to those described with acute treatment of influenza with the M2 channel inhibitors amantadine and rimantadine²⁷⁻³² and the topically applied neuraminidase inhibitor zanamivir.⁷⁻⁹ More rapid return to usual activities has also been reported following treatment with rimantadine^{30,33} and zanamivir.^{7,9}

Osetamivir was generally well tolerated in this study, although nausea and emesis occurred more frequently in treated individuals than in those receiving placebo. Nausea resolved without treatment and despite continuation of drug therapy and was not associated with an increase in discontinuation rates in treated individuals compared with placebo recipients. Drug administration with even small amounts of food appeared to prevent this effect.¹⁵ In pharmacokinetic studies, administration of drug with food was associated with increased absorption,¹³ so that alleviation of nausea by administration with food is consistent with gastric irritation rather than a central drug effect. No other adverse effects or laboratory value abnormalities were associated with osetamivir treatment.

Virus replication in the lower respiratory tract could not be assessed directly

in the current study, but the reduced duration of cough and rate of secondary bronchitis are consistent with preclinical studies showing that oral administration delivers sustained levels of osetamivir carboxylate throughout the respiratory tract, including the sinus cavities and middle ear,³⁴ and reduces lung virus titers in murine models.^{12,14} This suggests that oral administration of osetamivir results in antiviral effects in both the upper and lower respiratory tract.

A potential advantage of neuraminidase inhibitors over existing M2 inhibitors is their expanded spectrum of activity. In previous studies of zanamivir, reductions in the duration of illness were seen with both influenza A and B.⁷ Because of the low prevalence of influenza B in the 1997-1998 winter season, only 9 individuals infected with influenza B were enrolled in the study. However, results in these subjects were similar to those of the group as a whole (data not shown).

Antiviral drug resistance has been one factor that has limited more widespread use of amantadine and rimantadine.³⁵ Resistant viruses emerge rapidly and relatively frequently in individuals treated with these agents^{5,33} and can be transmitted to and cause disease in susceptible contacts.^{5,33,36} Antiviral resistance to neuraminidase inhibitors has been observed much less frequently in human studies to date, possibly because mutations in the conserved residues in the neuraminidase can be associated with decreased replication fitness.³⁷ One zanamivir-resistant virus with dual hemagglutinin and neuraminidase mutations has been reported in an immunosuppressed child receiving prolonged nebulized zanamivir for treatment of influenza B pneumonia³⁸; the specific mutations responsible for resistance in the virus isolated in our study have not yet been identified. However, the results of our study also suggest that emergence of resistance during short-term treatment of acute influenza in healthy adults may not be a clinically significant problem for the neuraminidase inhibitors.

Several potential limitations of this study should be considered. A substantial proportion of the 2120 individuals screened for enrollment did not meet the entry criteria for the study, because they did not have typical influenza symptoms, were not febrile, or had been ill for too long. Thus, the results of the study should be considered in the context of appropriately selective use of an antiviral drug for acute influenza. In addition, the study protocol specifically excluded individuals with medical conditions that are often associated with more severe influenza. However, assuming that the mechanism by which influenza causes illness in these individuals remains the same, there is little reason to think that the benefit of early treatment would not also be seen in a higher-risk population. As expected, the greatest benefit of therapy was seen in individuals with evidence of influenza virus infection. However, analysis of the entire population also demonstrated a significant benefit of treatment. In summary, our trial indicates that osetamivir is an effective treatment for acute influenza in healthy adults. The findings provide a rationale for continued study of this agent for the treatment of influenza, including studies in children and in high-risk populations.

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