Articles

Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial

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Summary

Background Use of some antiviral drugs for influenza infection is limited by potential rapid emergence of resistance. We studied the efficacy and safety of oseltamivir, the oral prodrug of the neuraminidase inhibitor GS4071, in adults with naturally acquired laboratory-confirmed influenza.

Methods We did a randomised controlled trial of 726 previously healthy non-immunised adults with febrile influenza-like illness of up to 36 h duration. Patients were assigned oral oseltamivir 75 mg (n=243), oseltamivir 150 mg (n=245), or placebo (n=238) twice daily for 5 days. We assessed recovery by questionnaire and temperature recordings. The primary endpoint was time to resolution of illness in influenza-infected patients.

Findings 475 (66%) patients had confirmed infection. Duration of illness was significantly shorter by 29 h (25% reduction, median duration 87·4 h [95% CI 73·3–104·7], p=0·02) with oseltamivir 75 mg and by 35 h (30%, 81·8 h [68·2–100·0], p=0·01) with oseltamivir 150 mg than with placebo (116·5 h [101·5–137·8]). The effect of oseltamivir was apparent within 24 h of the start of treatment. In patients treated within 24 h of symptom onset, symptoms were alleviated 43 h (37% reduction) and 47 h (40%) earlier with oseltamivir 75 mg and 150 mg, respectively, compared with placebo (75 mg 74·5 h [68·2–98·0], p=0·02; 150 mg 70·7 h [54·0–89·4], p=0·01; placebo 117·5 h [103·0–143·8]). Oseltamivir was associated with higher symptom scores, less viral shedding, and improved health, activity, and sleep quality, and was well tolerated.

Interpretation Oseltamivir was effective and well tolerated in the treatment of natural influenza infection in adults. The efficacy, tolerability, and ease of administration warrant further investigation in children, elderly patients, and at-risk patients.

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Introduction

Influenza continues to inflict an important burden on health-care systems, filling hospital beds during winter months and causing misery to millions of people worldwide. As well as the individual and direct health-care burden, work absenteeism during epidemics can have a substantial economic impact.[1–3] Although vaccination can lessen the impact of the disease in high-risk groups,[4,5] efficacy can be variable and unvaccinated populations remain vulnerable to disease. Antivirals represent a rational approach to influenza control but only the M2 inhibitors, amantadine and rimantadine, have been available. The use of these two drugs is limited by the potential for rapid emergence of resistant viruses capable of transmission to and causing disease in close contacts. Neither treatment is effective against influenza B, and amantadine has a side-effect profile that limits its use in frail elderly patients.[6] The goal of achieving broad activity against influenza viruses became possible with the discovery that one of the virus's surface proteins, the neuraminidase, possesses a highly conserved active site.[7]

Influenza neuraminidase is essential for viral replication. Through cleaving of terminal sialic-acid residues from glycoproteins, this enzyme facilitates the release of new virus particles from infected cells, prevents virus aggregation, and promotes viral passage through respiratory mucus.[8] Inhibition of the enzyme has become possible with the development of the neuraminidase inhibitors zanamivir[9] and GS4071 ([3R, 4R, 5S]-4-acetamido-5-amino-3-[1-ethylpropoxy]-1-cyclohexane-1-carboxylic acid),[10] which show potent and specific activity against a wide range of influenza-virus neuraminidases in vitro.[11,12] Zanamivir has poor oral bioavailability and has been developed for administration by inhalation,[13] a route that requires specific instructions to ensure adequacy of delivery. The oral prodrug of GS4071, oseltamivir, is highly bioavailable and undergoes rapid conversion to the active form after gastrointestinal absorption.[14]

Oral oseltamivir was effective in studies of experimental influenza in animals and human beings.[12,15,16] We did a double-blind randomised placebo-controlled study to investigate the efficacy and safety of oseltamivir in the treatment of naturally acquired influenza in human beings.

Methods

Patients

Eligible patients were aged 18–65 years and presented within 36 h of onset of influenza-like illness with fever of at least 38°C, with at least one respiratory symptom (cough, sore throat, or nasal symptom) and at least one constitutional symptom

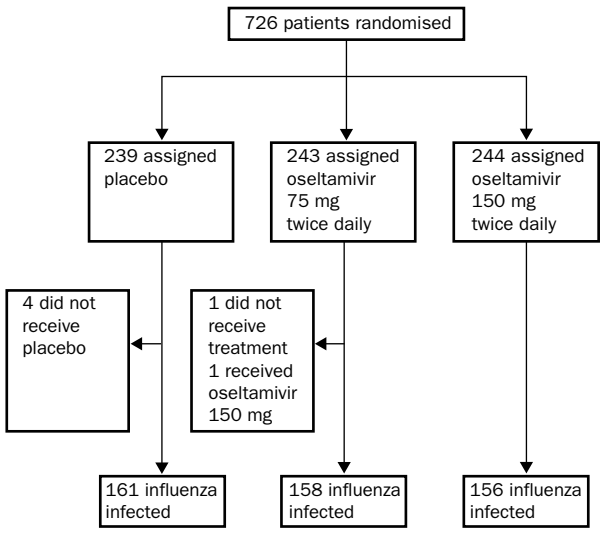

Figure 1: **Trial profile**

	Placebo	Oseltamivir 75 mg	Oseltamivir 150 mg
Safety population			
n	235	242	242
Mean (SD) age (years)	37·4 (11·9)	38·2 (11·1)	36·7 (11·8)
Male/female	50%/50%	50%/50%	53%/47%
Intention-to-treat population			
n	235	241	243
Infected	161 (69%)	158 (66%)	156 (64%)
Influenza-positive by culture only	22 (9%)	16 (7%)	25 (10%)
Influenza-positive by serology only	34 (15%)	23 (10%)	24 (10%)
Influenza-positive by culture and serology	105 (45%)	119 (49%)	107 (44%)
Influenza-infected population			
n	161	158	156
Influenza A	155 (96%)	153 (97%)	151 (97%)
Influenza B	6 (4%)	5 (3%)	5 (3%)
Mean (SD) oral temperature (°C)	38·5 (0·5)	38·6 (0·5)	38·6 (0·5)
Smokers	59 (37%)	54 (34%)	54 (35%)
Undetectable influenza serum antibody status (<1:10)	126 (84%)	130 (86%)	121 (85%)
Median (range) duration of illness before study entry (h)	23 (0–59)*	24 (4–60)*	25 (0–43)*
Median (range) symptom score at enrolment	15 (5–21)	15 (5–21)	14 (2–21)

*Six patients with entry into study >36 h after symptom onset were included in analysis.

Table 1: **Demographic characteristics of treated patients and clinical characteristics of influenza-infected patients**

(headache, malaise, myalgia, sweats or chills, or fatigue). All patients had to provide written informed consent and women had to have a negative urine pregnancy test. We excluded patients who had been vaccinated against influenza in the previous 12 months, had active clinically important chronic illness or known HIV-1 infection, were receiving steroids or other immunosuppressants, and who had a history of drug or alcohol abuse. We required that women of childbearing age use contraception.

Study design

We did the study in 51 centres in Europe, 11 in Canada, and one in China in January to March, 1998. We followed the principles of the Declaration of Helsinki (amended) and the requirements of local ethics committees.

We took medical histories, measured vital signs, did physical examinations, and collected baseline virological samples before treatment. Patients were randomly assigned oseltamivir 75 mg, oseltamivir 150 mg, or matching placebo twice daily for 5 days. Randomisation was computer generated by a central randomisation facility, which had sole access to the code. Each centre provided its own medication in individually numbered packs, according to the instructions of the randomisation centre. Patients self-administered the medication. We assessed compliance by daily diary cards and review of the returned medication at the end of treatment. Patients were provided with relief medication (paracetamol) at enrolment; they were asked to take it only as required for the relief of symptoms and to record its use and that of any other symptom-relief medication.

Assessments

Patients recorded their oral temperature and the presence and severity of influenza symptoms of cough, nasal obstruction, sore throat, fatigue, headache, myalgia, and feverishness on a four-point scale (0 absent, 1 mild, 2 moderate, and 3 severe) twice daily for up to 21 days. On each day during of treatment (days 1–5), patients recorded ability to do their normal activities, overall health status, and sleep quality on a ten-point visual analogue scale (0 unable to do normal activities, worst health, and worst sleep quality, 10 fully able to do normal activities, best possible health, and best possible sleep quality).

Influenza was confirmed by culture or serology; for culture of nose and throat samples, swabs were collected at baseline and, for most patients, on days 2, 4, 6, and 8. Nasopharyngeal samples were transported in 3 mL of viral transport medium within 24 h, on wet ice, to a central laboratory and immediately frozen at −70°C. Initial virus isolation and subsequent virus titrations were done in a single lot of tertiary cynomolgus monkey-kidney cells from separate nasopharyngeal samples of 750 μL for isolation and typing, 750 μL for titration of virus, 250 μL for genotyping, and 250 μL for phenotyping. We tested all samples for each patient simultaneously. Viral titres were calculated as $\log_{10}$ $TCID_{50}$/mL of viral transport medium by the Spearman-Karber equation. We also collected acute serum samples at enrolment and a convalescent sample at 21 days for haemagglutination-inhibition assays. These assays were done by standard methods with antigens known to be circulating during the 1997–98 influenza season (influenza A/Shenzen/95 [H1N1], A/Wuhan/95 [H3N2], A/Sydney/97 [H3N2], and B/Harbin/95).[17] A significant serum haemagglutination-inhibition response was defined as a four-fold or more rise in type-specific antibody between baseline and day 21. Treatment assignment was not known during virological testing, which was done at Erasmus University, Rotterdam.

The primary efficacy endpoint was the length of time to resolution of influenzal illness (defined as the period from start of study-drug to relief of symptoms) in the intention-to-treat population of infected patients. This population consisted of patients who had received at least one dose of study medication and who had laboratory-confirmed influenza, defined by virus isolation, a four-fold or more haemagglutination-inhibition response, or both. Symptom relief was taken to occur at the start of the first 24 h period in which all influenza symptoms were scored as mild or none and remained so for at least 24 h. Other endpoints included: time to resolution of influenzal illness for all randomised patients; severity of illness, defined as the area under the curve for total symptom scores, for the whole illness duration; health, activity, and sleep quality, defined as the area under curve for scale scores, for the whole the treatment period; the frequency of and need for antibiotic treatment for common complications of influenza (otitis media, bronchitis, sinusitis, and pneumonia); and virus shedding.

Statistical analysis

We calculated sample sizes from published data on the duration of influenza illness in similar trials of antiviral agents for the treatment of influenza.[18] A sample size of 190 assessable patients (85 infected) was required for 80% power and a significance level of 0·025 for the primary comparisons; we assumed that an overall two-sided 5% significance level was distributed equally between the comparisons of each dose of oseltamivir with placebo, with an SD of 3 days and a median difference of 1 day between groups, and that 50% of the recruited population would be influenza infected. Sample size calculations were done by normal approximation to Wilcoxon's rank sum test.

	Intention-to-treat population			Influenza infected		
	Placebo (n=235)	Oseltamivir 75 mg (n=241)	Oseltamivir 150 mg (n=243)	Placebo (n=161)	Oseltamivir 75 mg (n=158)	Oseltamivir 150 mg bid (n=156)
All patients						
Median (95% CI) duration of illness (h)	116·1 (99·8–129·5)	97·6 (79·1–115·3)	89·4 (79·1–103·7)	116·5 (101·5–137·8)	87·4 (73·3–104·7)	81·8 (68·2–100·0)
p	..	0·05*	0·03*	..	0·02*	0·01*
Median (range) total symptom score AUC	916·6 (0–5996·0)	851·3 (0–6069·0)	708·5 (0–5811·0)	943·0 (0–5408·0)	773·3 (0–3793·0)	708·5 (0–4797·0)
p	..	0·1†	0·03†	..	0·01†	0·003†
Median duration for return to normal sleep quality (h)	249 (204–367)	199 (158–252)	204 (156–247)	204 (179–275)	170 (151–223)	159 (147–221)
p	..	0·03‡	0·02‡	..	0·02‡	0·01‡
Median (range) scale score AUC						
Health	735 (105–1564)	804 (108–3530)	796 (48–3309)	746 (141–1411)	809 (108–3530)	806 (48–3309)
p	..	0·002†	0·007†	..	0·003†	0·0008†
Activity	690 (69–1595)	769 (0–3163)	762 (48–3237)	703 (69–1585)	787 (0–3163)	793 (108–3237)
p	..	0·008†	0·002†	..	0·02†	0·002†
Median (95% CI) time to alleviation of cough (h)	62 (46–72)	34 (23–48)	32 (22–42)	72 (62–99)	48 (30–61)	35 (22–44)
p	..	0·02	0·006	..	0·007	0·0001
Median (95% CI) time to become afebrile (≤37·2°C)	59 (48–68)	45 (38–52)	41 (33–46)	67 (56–74)	39 (31–45)	37 (31–44)
p	..	0·2	0·003	..	0·002	<0·0001
Median overall paracetamol (g)	3·0	3·0	2·0	3·0	2·5	2·0
Patients treated within 24 h						
Total	127 (54%)	130 (54%)	118 (49%)	83 (52%)	77 (49%)	66 (42%)
Median (95% CI) duration of illness (h)	114·6 (94·3–135·2)	76·8 (67·5–104·4)	80·0 (63·5–100·0)	117 (103·0–143·8)	74·5 (68·2–98·0)	70·7 (54·0–89·4)
p	..	0·03*	0·05*	..	0·02*	0·01*

AUC=area under curve. *Weighted Mantel-Haenszel test, adjusted for multiple comparisons. †Extended Wilcoxon's rank sum test. ‡Weighted Mantel-Haenszel test.

Table 2: **Duration and severity of illness in intention-to-treat population and influenza-infected patients**

For the primary-endpoint comparisons, we used a weighted Mantel-Haenszel test stratified for country, geographic area or continent, and smoking status. We investigated the consistency of treatment effects between regions and smoking groups. Patients who withdrew before symptoms resolved were censored at the time of withdrawal.

For the areas under curves for severity of illness and viral titre we compared the placebo group with each oseltamivir group by extended Wilcoxon's rank sum test. The data derived from the self-assessment scales for general-health status, activity, and sleep quality were summarised, and the area under curve (score×h) for each of the three scales was analysed for the whole dosing period. We did assessments according to the trapezoidal rule. Comparison of placebo with each active treatment was analysed by extended Wilcoxon's rank sum test, stratified for region and smoking status. We adjusted p values for multiple comparisons of treatment groups for the primary endpoint but not for other variables. All analyses were done on SAS software (version 6.12). We took differences with $p \leq 0{\cdot}05$ for two-tailed tests to be significant.

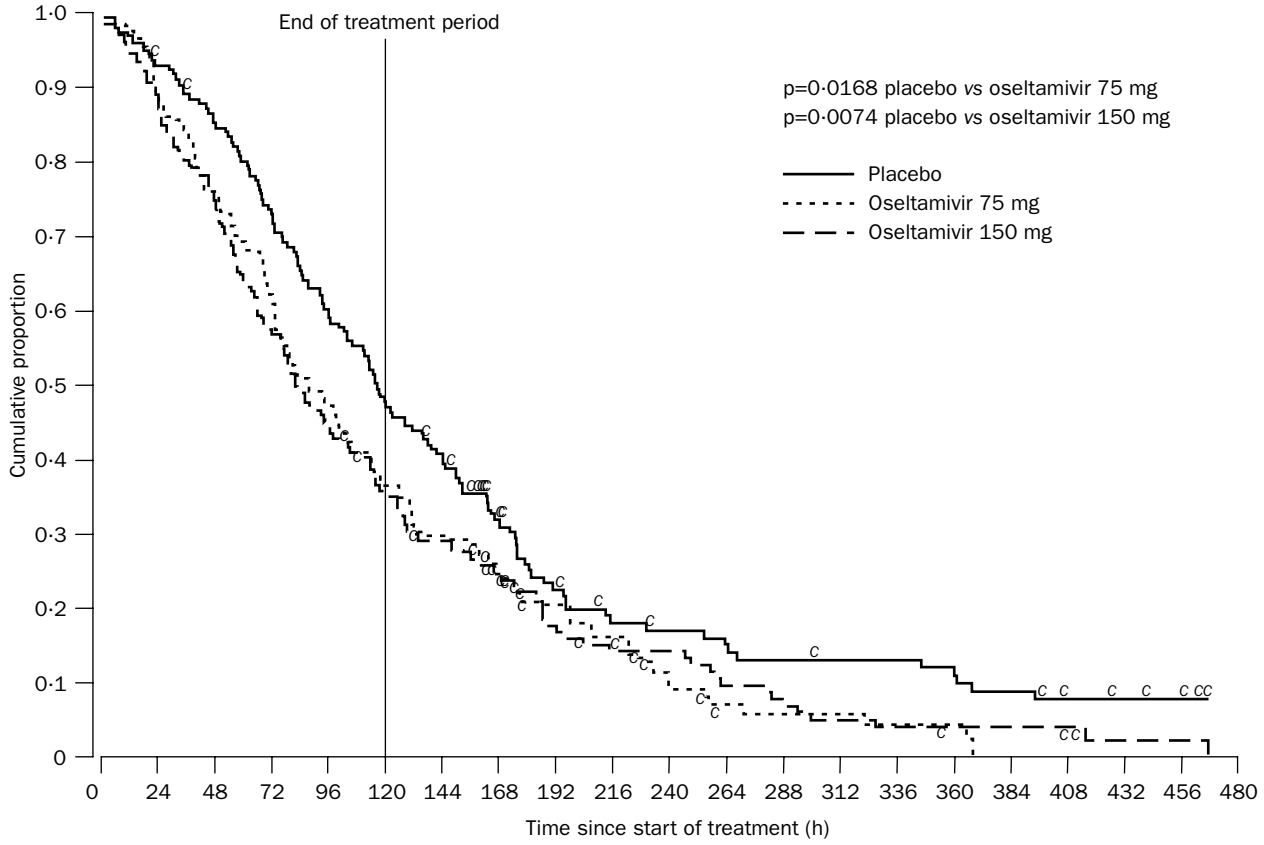

Figure 2: **Time (h) to resolution of all symptoms in influenza-infected patients**
c=censored patients who withdrew before resolution of symptoms.

	Placebo		Oseltamivir 75 mg		Oseltamivir 150 mg	
	Antibiotic	No antibiotic	Antibiotic	No antibiotic	Antibiotic	No antibiotic
Intention-to-treat population*						
Bronchitis	3 (1·3%)	2 (0·9%)	1 (0·4%)	6 (2·5%)	5 (2·1%)	3 (1·2%)
Otitis media	1 (0·4%)	0	0	0	0	1 (0·4%)
Pneumonia	1 (0·4%)	0	0	0	2 (0·8%)	0
Sinusitis	5 (2·1%)	1 (0·4%)	5 (2·1%)	4 (1·7%)	6 (2·5%)	3 (1·2%)
Any specified secondary illness†	10 (4·3%)	3 (1·3%)	6 (2·5%)	10 (4·1%)	12 (4·9%)	7 (2·9%)
Influenza-infected population‡						
Bronchitis	2 (1·2%)	1 (0·6%)	0	5 (3·2%)	2 (1·3%)	3 (1·9%)
Otitis media	0	0	0	0	0	1 (0·6%)
Pneumonia	1 (0·6%)	0	0	0	0	0
Sinusitis	5 (3·1%)	1 (0·6%)	1 (0·6%)	3 (1·9%)	4 (2·6%)	3 (1·9%)
Any specified secondary illness†	8 (5·0%)	2 (1·2%)	1 (0·6%)	8 (5·1%)	5 (3·2%)	7 (4·5%)

*Placebo n=235, oseltamivir 75 mg n=241, oseltamivir 150 mg n=243. †Specified illnesses: bronchitis, otitis, pneumonia, and sinusitis starting ⩾48 h after first dose. ‡Placebo n=161, oseltamivir 75 mg n=158, oseltamivir 150 mg n=156.

Table 3: **Effect of oseltamivir treatment on antibiotic use**

Results

726 patients were enrolled into the study (figure 1); seven took no study medication (confirmed by capsule counts) and were excluded from all analyses. 719 received at least one dose of assigned medication (table 1, figure 1). Overall, 475 (66%) of the 719 patients had laboratory-confirmed influenza (161 placebo, 158 oseltamivir 75 mg, 156 oseltamivir 150 mg, table 1), mostly (92%) H3N2 strains of influenza A. 38 patients withdrew from the study—15 because of adverse events (six placebo, three oseltamivir 75 mg, six oseltamivir 150 mg), and 23 were lost to follow-up (three oseltamivir 150 mg), withdrew for personal reasons (five placebo, one oseltamivir 75 mg, four oseltamivir 150 mg), or were withdrawn for protocol violations (four placebo, four oseltamivir 75 mg, one oseltamivir 150 mg) or for early improvement (one oseltamivir 150 mg). All available data from these patients were included in the efficacy and safety analyses. Safety of study drug was assessed for all 719 patients. The 475 patients who were infected with influenza were included in the primary-endpoint analysis. About 85% of the influenza-infected population were culture positive across the three treatment groups. Patients' characteristics were well distributed across treatment groups (table 1). Only 16 (3%) patients were infected with influenza B (six, five, and five patients in the placebo, 75 mg, and 150 mg groups, respectively). This number was insufficient for a meaningful analysis of effect against naturally acquired influenza B.

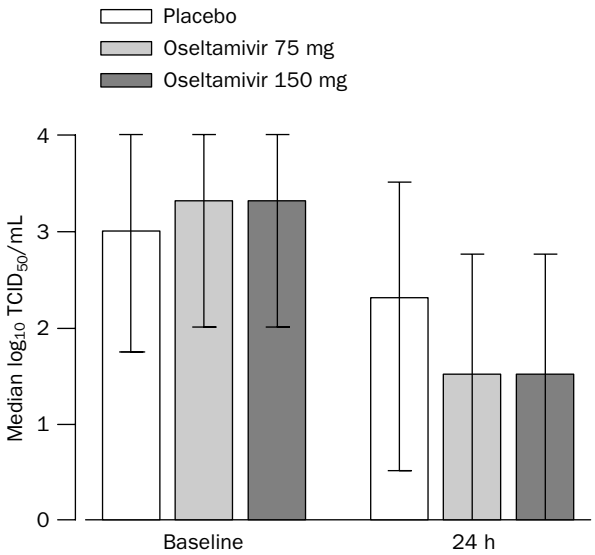

Figure 3: **Median virus titre (log_{10} $TCID_{50}$/mL)**
Data from 350 people who provided nasopharyngeal samples before and at 24 h, 72 h, and 120 h after start of treatment. Vertical bars show IQR. Oseltamivir 75 mg *vs* placebo p=0·0004, oseltamivir 150 mg *vs* placebo p=0·0003 for change from baseline.

In patients with laboratory-confirmed influenza, the median duration of illness was significantly shorter in the 75 mg group, by 29 h (25% reduction, median duration 87·4 h [95% CI 73·3–104·7], p=0·02]), and in the 150 mg group, by 35 h (30%, 81·8 h [68·2–100·0], p=0·01]), than in the placebo group (116·5 h [101·5–137·8]; table 2). This treatment effect was consistent across the subgroups analysed by country, geographic area or continent, and smoking status, and was apparent as early as 24 h after the start of treatment (figure 2). The median illness duration was also significantly lower in the intention-to-treat population than in the other subgroups (75 mg group 97·6 h [79·1–115·6], p=0·05; 150 mg group 89·4 h [79·1–103·7], p=0·03; placebo, 116·1 h [99·8–129·5]). The duration of illness was significantly lower in the intention-to-treat population than in the other subgroups because of the high proportion of influenza-infected patients in this population.

In 226 influenza-infected patients who were assigned treatment within 24 h of symptom onset, symptoms improved 43 h and 47 h earlier in the 75 mg and 150 mg groups, respectively, than in the placebo group (75 mg, 37%, 74·5 h [68·2–98·0], p=0·02; 150 mg 40%, 70·7 h [54·0–89·4], p=0·01; placebo 117·5 h [103·0–143·8]; table 2). There were 74, 83, and 87 individuals without confirmed influenza infection in the placebo, 75 mg, and 150 mg groups, respectively. Median durations of illness were, placebo 116·1 h (81·9–139·0), 75 mg 126·3 h (81·0–151·5, p=0·93), and 150 mg 99·5 h (80·0–139·6, p=0·93).

Total areas under curves for symptom scores were significantly lower in influenza-infected patients assigned oseltamivir than in those assigned placebo (table 2). Compared with the placebo group, oseltamivir recipients reported improved health and ability to do normal activities and had less sleep disturbance during the treatment period (days 1–5, table 2). Cough resolved a median of 24 h and 37 h earlier in the oseltamivir 75 mg and 150 mg groups, respectively, compared with placebo (table 2). The time to become afebrile (temperature ⩽37·2°C) was significantly shorter and relief medication generally used less in the oseltamivir groups than in the placebo group (table 2), but the differences were not significant. Antibiotics to treat medically diagnosed complications were also generally used less in the oseltamivir group, but we did no statistical analysis of this variable since antibiotics were prescribed infrequently (table 3).

Virology

Data on viral shedding were available for 350 influenza-infected patients. Median virus titre areas under curves were lower by 30–40% during the first 4 days of treatment in the oseltamivir groups than in the placebo group (75 mg group, 78·2 $\log_{10}$ $TCID_{50}$×h/mL, p=0·03; 150 mg group, 94·4 $\log_{10}$ $TCID_{50}$×h/mL, p=0·003; placebo group, 130·8 $\log_{10}$ $TCID_{50}$×h/mL). The differences were greater in virus titres in nose and throat swabs of patients treated with oseltamivir than in those treated with placebo at 24 h after the start of treatment (figure 3). Patients treated with oseltamivir showed similar increases in haemagglutination-inhibition antibody titre to placebo recipients (data not shown).

Tolerability

Oseltamivir was generally well tolerated compared with placebo, with no increase in study withdrawal rates because of adverse events. Transient upper-gastrointestinal events generally occurred at the start of treatment and resolved within 1–2 days and were more frequent in the oseltamivir groups than in the placebo group (nausea: 75 mg group mean frequency 12% [range 2·9–12·6%], 150 mg group 12% [2·5–12·1%], placebo group 4%; vomiting: 10% [2·6–11·3%], 9% [1·9–10·3%], and 3%). Laboratory results and vital signs did not differ significantly from baseline for the two oseltamivir groups or the placebo group. There was only one striking laboratory abnormality (neutropenia $\leq 0{\cdot}59\times10^9$/L in a placebo recipient).

Discussion

The administration of oral oseltamivir 75 mg or 150 mg twice daily was associated with significant clinical and antiviral effects in healthy adults with naturally occurring influenza and was generally well tolerated. For patients with documented influenza, the median time to resolution of illness was reduced by 25% in the 75 mg group and by 30% in the 150 mg group.

The shorter duration of illness in oseltamivir recipients was associated with similar improvements in the severity of illness and confirms results from a challenge study, which also showed lower viral titres and shorter duration of illness.[16] The improvement of symptoms in our study was apparent within 24 h of oseltamivir administration, which was during the acute phase of illness when influenza symptoms are generally most troublesome. The decreases in the severity and duration of illness by oseltamivir were accompanied by higher scores in patients' self-assessment of their health and activity, and by less sleep disturbance. The magnitude of the clinical benefit occurred despite the unrestricted use of paracetamol, which has analgesic and antipyretic properties. Overall, paracetamol use was lower in the oseltamivir groups than in the placebo group, which shows that symptoms were not improved because of the use of relief medication. Although we did not assess economic effects, the clinical benefits in the influenza-infected and intention-to-treat populations could lower the indirect costs of influenza, such as workplace absenteeism and performance at work.[3,19]

Patients with virologically confirmed influenza who began treatment within 24 h of onset of symptoms had the greatest benefit; their illness was alleviated about 2 days earlier than with placebo. Similarly, illness in the intention-to-treat population was alleviated about 1·5 days earlier than with placebo. These findings are consistent with results from studies of other antiviral drugs for influenza and other self-limiting viral diseases, for which increased therapeutic benefit is obtained when treatment is started as early as possible after symptom onset.[18,20,21]

The principle site of influenza virus replication in human beings is the respiratory-tract epithelium. Complications of influenza are mostly respiratory[22] and contribute substantially to the morbidity and mortality associated with disease.[4,23] The primary outcome variable decided our sample-size calculation and the study was too small to detect differences in the incidence of complications of the upper and lower respiratory tract for which antibiotics were prescribed. The duration of cough was, however, significantly shortened and the severity of cough (data not shown) and the frequency of antibiotic use for complications generally lower in the oseltamivir groups.

Influenza is transmitted by virus-laden secretions. Cough can be one of the most distressing symptoms of influenza and also contributes to the spread of infection. Patients who received oseltamivir had significantly lower titres than those in the placebo group of virus on nose-throat swabs. Although not tested, such differences, together with improvement of symptoms, including cough, might reduce transmission of the virus. Importantly, despite antiviral effects, oseltamivir did not impair the humoral immune response to infection, which implies that oseltamivir recipients have the same immunity to reinfection as untreated individuals.

The clinical and virological benefits seen with oseltamivir might accrue from the broad exposure to the drug in the whole respiratory tract and other tissues. Whole-body radiography in ferrets has shown distribution of GS4071 throughout the respiratory tract and middle ear after oral administration of oseltamivir.[24] Several investigators have noted the occasional presence of influenza A and B, viral RNA, or viral antigens at extrapulmonary sites, including the blood, brain, cerebrospinal fluid, liver, muscle, and amniotic and middle-ear fluids. The widespread distribution of GS4071 offers a theoretical advantage over inhaled zanamivir that needs to be established in future studies.

Oral oseltamivir was generally well tolerated at the two doses we studied. The most common adverse events were nausea and vomiting at the start of treatment, which were generally mild to moderate and resolved in 1–2 days. The groups did not differ for early withdrawal from the study.

We did not design this study to compare the activity of the two dose groups; the effects did not differ between doses for magnitude of clinical and antiviral effects. The efficacy, tolerability, and ease of administration of oseltamivir in healthy adults with uncomplicated influenza reinforce its further investigation in children, in the elderly, and in populations at high risk.

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