Journal of Antimicrobial Chemotherapy Advance Access published January 7, 2011

J Antimicrob Chemother
doi:10.1093/jac/dkq511

Journal of Antimicrobial Chemotherapy

Impact of early oseltamivir treatment on outcome in critically ill patients with 2009 pandemic influenza A

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Received 8 October 2010; returned 9 November 2010; revised 2 December 2010; accepted 6 December 2010

Objectives: The impact of oseltamivir on mortality in critically ill patients with 2009 pandemic influenza A (2009 H1N1) is not clear. The main objective of this study was to investigate the relationship between the timing of antiviral administration and intensive care unit (ICU) outcomes.

Methods: Prospective, observational study of a cohort of ICU patients with confirmed 2009 H1N1 infection. Clinical data, treatment and outcome were compared between patients receiving early treatment (ET) with oseltamivir, initiated within 2 days, and patients administered late treatment (LT), initiated after this timepoint. Multivariate analysis and propensity score were used to determine the effect of oseltamivir on ICU mortality.

Results: Six hundred and fifty-seven patients were enrolled. Four hundred and four (61.5%) patients required mechanical ventilation (MV; mortality 32.6%). Among them, 385 received effective antiviral therapy and were included in the study group. All patients received oseltamivir for a median duration of 10 days (interquartile range 8–14 days). Seventy-nine (20.5%) ET patients were compared with 306 LT patients. The two groups were comparable in terms of main clinical variables. ICU length of stay (22.7±16.7 versus 18.4±14.2 days; $P=0.03$), hospital length of stay (34.0±20.3 versus 27.2±18.2 days; $P=0.001$) and MV days (17.4±15.2 versus 14.0±12.4; $P=0.04$) were higher in the LT group. ICU mortality was also higher in LT (34.3%) than in ET (21.5%; OR=1.9; 95% CI 1.06–3.41). A multivariate model identified ET (OR=0.44; 95% CI 0.21–0.87) as an independent variable associated with reduced ICU mortality. These results were confirmed by propensity score analysis (OR=0.44; 95% CI 0.22–0.90; $P<0.001$).

Conclusions: Our findings suggest that early oseltamivir administration was associated with favourable outcomes among critically ill ventilated patients with 2009 H1N1 virus infection.

Keywords: antiviral treatment, prognosis, pneumonia

Introduction

Infection with a novel influenza A H1N1 strain, 2009 pandemic influenza A (2009 H1N1), emerged in late March 2009[1] and spread rapidly to all continents, causing >18000 deaths according to WHO reports.[2] Patients with 2009 H1N1 infection who required admission to intensive care units (ICUs) were more frequently young,[3–5] obese[6–8] or pregnant women.[9,10] The pathogenesis of influenza illness suggests that inhibiting viral replication as early as possible after infection onset might

reduce the duration and the intensity of clinical symptoms. Observational studies[8,11,12] reported that starting antiviral therapy within 2 days of illness onset was associated with a better outcome. However, these studies included only a small number of patients requiring ICU admission.

The present study in a cohort of critically ill patients with 2009 H1N1 infection aimed to investigate the relationship between the time of antiviral administration and ICU mortality as a primary endpoint, and also to determine whether early administration of oseltamivir affects the duration of mechanical ventilation (MV) and ICU/hospital length of stay (LOS).

Methods

This prospective, observational cohort study of ICU patients was conducted in 148 ICUs in Spain. Data were obtained from a voluntary registry between 23 April and 31 December 2009, managed by the Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC). Inclusion criteria were: fever (>38°C); respiratory symptoms consistent with cough, sore throat, myalgia or influenza-like illness; acute respiratory failure requiring ICU admission; and microbiological confirmation of 2009 H1N1 infection. Data were reported by the attending physician reviewing medical charts and radiological and laboratory records. Children <15 years old were not enrolled in this registry. The study was approved by the Ethics Committee of Joan XXIII University Hospital, Tarragona (Spain). Patient identification remained anonymous and the informed consent requirement was waived due to the observational nature of the study. All tests and procedures were ordered by the attending physician.

The following variables were recorded: demographic data; co-morbidities; time of illness onset and hospital admission; time to first dose of antiviral delivery; microbiological findings; and chest radiological findings at ICU admission. To determine the severity of illness, the Acute Physiology and Chronic Health Evaluation (APACHE) II score[13] was determined in all patients within 24 h of ICU admission. Organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) scoring system,[14] also at ICU admission.

Definitions

The definition of community-acquired pneumonia was based on current American Thoracic Society and Infectious Diseases Society of America guidelines.[15] Patients who presented healthcare-associated pneumonia were excluded from the present study.[15] Nasopharyngeal swab specimens were collected at admission and lower respiratory secretions were also obtained in intubated patients. Real-time RT–PCR testing was performed in accordance with the CDC's published guidelines.[16] Testing of 2009 H1N1 virus was performed in each institution or centralized in a reference laboratory when not available. A 'confirmed case' was defined as an acute respiratory illness with laboratory-confirmed 2009 H1N1 infection identified by RT–PCR or viral culture.[5] Only confirmed cases were included in the current study.

Primary viral pneumonia was defined in patients presenting illness with acute respiratory distress and unequivocal alveolar opacities involving two or more lobes with negative respiratory and blood bacterial cultures during the acute phase of influenza virus infection.[5] Obese patients were defined as those with a body mass index (BMI) of >30 kg/m^2 and patients with BMI of >40 kg/m^2 were considered morbidly obese.[6]

Community-acquired respiratory co-infection (CARC) was considered in patients with confirmation of influenza virus infection showing recurrence of fever, increase in cough and production of purulent sputum plus positive bacterial/fungal respiratory or blood cultures.[5,17] Oseltamivir was administered orally or by nasogastric route in accordance with CDC recommendations and the regimen (150 mg/24 h or 300 mg/24 h) was chosen by the attending physician.[18] Intravenous zanamivir was not authorized for treatment of 2009 H1N1 in Spain at the time of the present study; however, compassionate use of zanamivir was allowed as rescue therapy in some of the centres.

Effective antiviral therapy was defined as a course of therapy with an antiviral drug (oseltamivir) active against the 2009 H1N1 virus for more than four doses after ICU admission.[5] Patients who received four or fewer doses were included in the whole population analysis, but only patients with effective antiviral therapy were considered in the assessment of the impact of antiviral therapy on outcome. Oseltamivir therapy was considered early treatment (ET) if the patients received treatment within 2 days of the onset of influenza symptoms and late treatment (LT) if the antiviral therapy commenced >2 days after onset of symptoms.

Shock was defined as the need for vasopressor drugs for >4 h after fluid replacement at the time of ICU admission.[19] The ICU admission criteria and treatment decisions for all patients, including determination of the need for intubation and type of antibiotic and antiviral therapy administered, were not standardized between centres and were left to the discretion of the attending physician.

Statistical analysis

Discrete variables are expressed as counts (percentage) and continuous variables as means ± SD or medians with interquartile range (IQR). For the demographic and clinical characteristics of the patients, differences between groups were assessed using the χ^2 test and Fisher's exact test for categorical variables, and the Student's *t*-test or Mann–Whitney *U*-test for continuous variables. The number of patients needed to treat (NNT) to prevent one patient having the target event (mortality) expresses the magnitude of a treatment effect. The NNT was calculated as the inverse of absolute risk reduction caused by treatment.[20]

Stepwise logistic regression models were used to adjust the estimated impact of antiviral therapy on ICU mortality for covariates that might be potential confounders. The variables were included in the multivariate analysis if they were significant in the univariate analysis ($P<0.05$), if they were in our hypothesis or if they were clinically significant. Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). Potential explanatory variables were checked for collinearity prior to inclusion in the regression models using the Tolerance and Variance Inflation Factor.

The effectiveness of early oseltamivir treatment (≤2 days) was estimated using propensity scores.[21] The goal of the propensity score was to balance the covariates observed among subjects in order to mimic the situation of a randomized study[22] and thus create a quasi-randomized experiment from a non-randomized observational study.[22] In our study, propensity scores were estimated by fitting a logistic regression. The covariates included in the propensity score model were the ones that presented significant differences in the univariate analysis (see Table 4). Propensity score quintiles were derived and, in order to assess the validity of the propensity scores, box plots of the estimated propensity scores were plotted for treated and untreated patients within each quintile. Finally, we fitted a logistic model for mortality including the propensity score quintiles and treatment as covariates. For all analyses, *P* values of <0.05 were considered significant. Data analysis was performed using SPSS for Windows 15.0 (SPSS, Chicago, IL, USA).

Results

Whole population

This was a secondary analysis enrolling 657 patients (Figure 1). Patients were relatively young (mean age 44.7 ± 14.6 years)

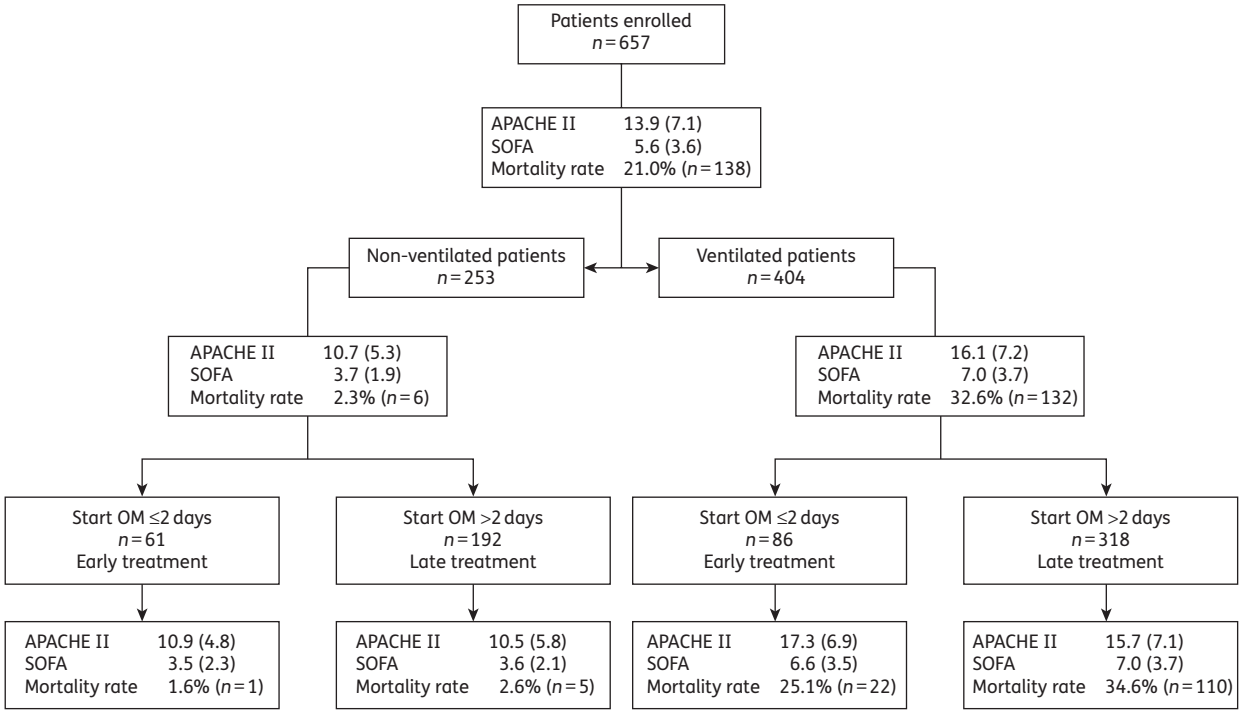

Figure 1. Flowchart of 657 critically ill patients enrolled in the study with 2009 H1N1 virus infection. OM, oseltamivir.

Table 1. Baseline demographic and clinical characteristics of the whole population of patients with 2009 H1N1 virus infection

Variable	
Age, years, mean (SD)	44.7 (14.6)
Male, *n* (%)	378 (57.2)
APACHE II score at day 1, mean (SD)	13.9 (7.1)
SOFA score at day 1, mean (SD)	5.6 (3.6)
Time between onset of 2009 H1N1 symptoms and hospital admission, days, mean (SD)	4.3 (2.6)
Quadrants infiltrated in chest X-ray at ICU admission, mean (SD)	2.3 (1.2)
Co-infection at ICU admission, *n* (%)	110 (16.6)
Shock at ICU admission, *n* (%)	295 (44.6)
Invasive mechanical ventilation, *n* (%)	404 (61.1)
Prone ventilation, *n* (%)	95 (14.4)
Steroid therapy at ICU admission, *n* (%)	265 (40.1)
Oseltamivir regimen (300 mg/day) at ICU admission, *n* (%)	452 (68.8)
Co-morbidities, *n* (%)	
asthma	81 (12.3)
chronic obstructive pulmonary disease	108 (16.3)
cardiovascular disease	47 (7.1)
haematological disease	40 (6.1)
pregnancy	31 (4.7)
obesity	238 (36.0)
diabetes mellitus	82 (12.4)
HIV infection	13 (2.0)
neuromuscular disease	24 (3.6)
ICU mortality, *n* (%)	138 (21.0)

and 57.2% ($n=378$) were male. The mean APACHE II score was 13.9 ± 7.1 and the mean SOFA score was 5.6 ± 3.6 with an ICU mortality of 21.0% ($n=138$). The baseline characteristics of the whole population are shown in Table 1. All patients received empirical antibiotic therapy in accordance with local protocols. Dual antibiotic therapy was received by 88.1% ($n=579$) of the patients and 24.9% of these received dual antibiotic therapy with a macrolide. No differences were observed in the number of antibiotics administered in survivors (median=2; IQR 2–2) and non-survivors (median=2; IQR 2–2). However, survivors received more frequent dual antibiotic therapy with macrolide (26.9%) than non-survivors (17.6%; $P=0.02$). Four hundred and fifty-two (68.8%) patients received high doses (300 mg/day) of oseltamivir. In the whole population, 22.3% ($n=147$) received early antiviral therapy (ET). Patients with late oseltamivir therapy (LT) received a higher number of antibiotics (1.9 ± 0.5) than patients with ET (1.8 ± 0.6; $P=0.01$). CARC was not more frequent in patients who received early oseltamivir therapy (12.9% versus 17.4%; $P=0.20$). However, a trend towards higher ICU mortality was observed in the LT group (23.1% versus 15.9%; OR for death=1.45; 95% CI 0.96–2.21; $P=0.06$). Table 2 compares ICU mortality in the whole population and other subgroups.

Obesity was the most frequent co-morbidity. Obese patients were more likely to receive higher doses of oseltamivir than non-obese patients (76.9% versus 64.9%; $P=0.003$). In addition, high doses of oseltamivir were more frequent in morbidly obese patients (87.1% versus 69.3%; $P<0.001$). ICU mortality did not differ between patients with or without obesity (20.2% versus 24.4%; $P=0.23$) or between those with or without morbid obesity (24.1% versus 24.8%; $P=0.99$).

Table 2. Differences in ICU mortality rate in the whole population and the other subgroups of the study

Population	ICU mortality (%)		Difference in mortality rate (%)	OR	95% CI	*P* value
	early treatment	late treatment				
Whole	15.9	23.1	7.2	1.45	0.96–2.21	0.06
Non-ventilated	1.6	2.6	1.0	1.65	0.19–13.9	0.62
Invasive ventilated	25.1	34.6	9.5	1.34	0.90–1.97	0.08
Study group	21.5	34.3	12.8	1.90	1.06–3.41	0.04

Non-ventilated patients

Two hundred and fifty-three patients did not require invasive MV. On ICU admission, their mean APACHE II score was 10.7±5.3 and their mean SOFA score was 3.7±1.9; ICU mortality rate was 2.3%. In this subgroup of patients, 61 (24.1%) received ET. No differences were observed in the severity of illness score on ICU admission (APACHE II score 10.9±4.8 versus 10.5±5.8; $P=0.64$), multiorgan dysfunction score (SOFA score 3.5±2.3 versus 3.6±2.1; $P=0.61$) and ICU mortality (1.6% versus 2.6%; $P=0.62$) between patients receiving ET and LT (Figure 1).

Ventilated patients

Four hundred and four patients required invasive MV. The severity of illness on ICU admission (APACHE II score 16.1±7.2; $P<0.001$), organ dysfunction (SOFA score 7.0±3.7; $P<0.01$) and ICU mortality rate (32.6%; $P<0.01$) were significantly higher than in non-ventilated patients (Figure 1). Eighty-six of the mechanically ventilated patients (21.3%) received ET. Severity of illness (APACHE II score) was higher in the ET group (17.3±6.9) than in the LT group (15.7±7.1; $P<0.005$). In contrast, organ dysfunction (SOFA score) was higher in the LT (7.0±3.7) than in the ET group (6.6±3.5; $P=0.013$). A trend towards higher ICU mortality was observed in the LT group (34.6% versus 25.1%; OR for death=1.34; 95% CI 0.90–1.97; $P=0.08$) (Table 2).

Ventilated patients with effective antiviral therapy

To determine the impact of oseltamivir therapy administration on mortality, patients receiving more than four doses of antiviral therapy were considered effectively treated and included in the present analysis. Among mechanically ventilated patients, 19 (4.7%) received less than four doses of antiviral treatment and were excluded. Finally, 385 mechanically ventilated patients were included in the present analysis, forming the study group. The severity of illness on ICU admission (APACHE II 27.8±10 versus 15.6±6.6; $P<0.01$), multiorgan dysfunction (SOFA score 12.0±5.4 versus 6.8±3.5; $P<0.01$) and ICU mortality rate (84% versus 31.7%; $P<0.01$) were higher in the patients excluded than in those included in the study.

In the study group, the mean APACHE II score on ICU admission was 15.4±6.6 (median=15; IQR 11–19), the mean SOFA score was 6.6±3.5 (median=6; IQR 4–9) and 57.6% of the sample ($n=222$) were male. All patients received oseltamivir therapy for a median duration of 10 days (IQR 8–14). The mean interval between symptoms onset and the first dose of oseltamivir therapy was 4 days (IQR 3–6). Oseltamivir therapy was empirically administered in 67.3% ($n=223$) of patients and 286 (74.3%) patients received high doses (300 mg/day).

Only 79 (20.5%) patients received ET. These patients were compared with 306 patients receiving LT. The baseline characteristics of patients included in both groups are shown in Table 3. The two groups were comparable in terms of age, severity of illness, multiple organ dysfunctions, number of quadrants infiltrated in the chest X-rays, requirement for vasoactive drugs due to shock, prone ventilation, high-dose oseltamivir regimen and steroid therapy (Table 3). Only asthma was more frequent in patients with ET (20.5% versus 7.6%; $P=0.03$). In the entire population, MV lasted 16.6±14.5 days (median=12; IQR 7–21.5). Patients with LT required 3 days more MV than ET (median=13 versus 10 days; $P=0.01$). ICU LOS in survivors was 21.6±16.1 days (median=17; IQR 11–30) and hospital LOS was 32.3±19.9 days (median=28; IQR 18–40). Both ICU and hospital LOS were significantly higher in LT than ET patients, by 4 and 7 days, respectively (Table 3).

Overall ICU mortality was 31.6% ($n=122$) and was significantly higher in LT (34.3%) than in ET patients (21.5%; OR=1.9; 95% CI 1.06–3.41). ICU mortality did not differ significantly between ventilated patients who presented co-morbidities and those who did not (33.1% versus 25.0%; $P=0.12$). No differences in ET (18.5% versus 22.0%; $P=0.50$) or in LT (81.1% versus 75.5%; $P=0.44$) were found in patients with and without obesity.

The NNT in the full cohort to save one life was estimated to be NNT=8 and was lower for patients who presented co-morbidities (NNT=5) than for those who did not (NNT=10). When only patients with LT were evaluated, no significant differences in ICU mortality were observed between patients with and without co-morbidities and between those in whom antiviral administration was started before or after 4 days (data not shown). Diabetes mellitus was documented in 46 patients and did not influence outcomes (Table 3). When the impact of early oseltamivir treatment was studied according to different age breakpoints (<40, 41–60 or >60 years), no significant differences were observed when all the age groups were included (data not shown).

The characteristics of patients at ICU admission according to survival or death are shown in Table 4. Patients who died presented higher APACHE II (18.4±7.2 versus 14.4±5.9; $P<0.001$) and SOFA (8.0±3.8 versus 6.3±3.2; $P<0.001$) scores at ICU admission. No differences in co-morbidities were observed, except for haematological disease, which was more frequent in non-survivors (13.9% versus 3.4%;

Table 3. Baseline demographic and clinical characteristics of 385 adult ventilated patients with effective antiviral therapy according to start of oseltamivir treatment

Variable	Time between onset of 2009 H1N1 symptoms and start of oseltamivir		
	≤2 days ($n=79$)	>2 days ($n=306$)	*P* value
Age, years, mean (SD)	47.4 (13.9)	44.7 (14.5)	0.08
Male, *n* (%)	47 (59.5)	175 (57.2)	0.70
APACHE II score at day 1, mean (SD)	16.8 (6.3)	15.3 (6.7)	0.06
SOFA score at day 1, mean (SD)	6.4 (3.2)	6.9 (3.6)	0.42
Time between onset of 2009 H1N1 symptoms and hospital admission, days, mean (SD)	2.6 (2.0)	4.5 (2.5)	0.001
Quadrants infiltrated in chest X-ray at ICU admission, mean (SD)	2.6 (1.2)	2.6 (1.0)	0.91
Co-infection at ICU admission, *n* (%)	11 (13.9)	61 (19.9)	0.28
Shock at ICU admission, *n* (%)	55 (69.6)	197 (64.8)	0.41
Prone ventilation, *n* (%)	19 (24.1)	72 (23.7)	0.88
Steroid therapy at ICU admission, *n* (%)	40 (50.6)	126 (41.2)	0.37
Oseltamivir regimen (300 mg/day) at ICU admission, *n* (%)	63 (79.7)	223 (72.8)	0.21
Co-morbidities, *n* (%)			
asthma	16 (20.5)	22 (7.6)	0.03
chronic obstructive pulmonary disease	20 (25.3)	52 (17.0)	0.10
cardiovascular disease	6 (7.6)	22 (7.6)	0.99
haematological disease	8 (10.1)	18 (5.9)	0.20
pregnancy	3 (3.8)	17 (5.7)	0.77
obesity	29 (36.7)	127 (42.3)	0.36
diabetes mellitus	13 (16.5)	33 (10.9)	0.16
HIV infection	1 (1.3)	6 (2.0)	0.34
neuromuscular disease	1 (1.3)	4 (1.3)	0.99
ICU LOS, days			
mean (SD)[a]	18.4 (14.2)	22.7 (16.7)	0.03
median (IQR)	14 (8.75–24)	17 (11–30)	
Hospital LOS, days			
mean (SD)[a]	27.2 (18.2)	34.0 (20.3)	0.001
median (IQR)	23 (13.75–36)	30 (20–43)	
Days of MV			
mean (SD)[a]	14.0 (12.4)	17.4 (15.2)	0.04
median (IQR)	10 (5–18.25)	13 (8–23)	
ICU mortality, *n* (%)	17 (21.5)	105 (34.3)	0.03

LOS, length of stay; MV, mechanical ventilation.
[a]Only for survivors.

$P<0.001$). Development of shock (73.8% versus 62.0%; $P=0.02$), number of quadrants infiltrated in chest X-ray (3.0 ± 1.0 versus 2.4 ± 1.1; $P<0.001$) and need for prone ventilation (32.8% versus 19.8%; $P<0.05$) were more frequently observed in non-survivors. Early oseltamivir therapy was more frequently administered in survivors (23.6%) than in non-survivors (13.9%; $P=0.02$) (Table 4).

Stepwise logistic regression models were used to determine the impact of antiviral therapy administration on ICU mortality when adjusted for potential confounding factors. The covariates with significant differences in the univariate analysis were included in the model (APACHE II score, SOFA score, quadrants infiltrated in chest X-ray, haematological disease, shock, prone ventilation, co-infection and early oseltamivir treatment) (Table 4). Multivariate analysis confirmed that early oseltamivir administration was independently associated with better survival rates (OR for death=0.44; 95% CI 0.21–0.87; Table 5) with a Hosmer–Lemeshow goodness-of-fit test score of 4.67 ($P=0.79$) for the model.

A propensity score analysis was performed to verify and validate these results. The outcome was highly consistent with the previous results (OR for death=0.44; 95% CI 0.22–0.90; $P<0.001$). Moreover, the distributions of the propensity scores for treated and untreated patients within each propensity score quintile were generally similar, reinforcing the validity of the results (Figure 2).

Table 4. Comparison of baseline demographic and clinical characteristics of 385 ventilated patients with 2009 H1N1 virus infection—survivors versus non-survivors

Variable	Survivors ($n=263$)	Non-survivors ($n=122$)	*P* value
Age, years, mean (SD)	44.6 (13.9)	48.0 (16.1)	0.11
Male, *n* (%)	145 (55.1)	78 (63.9)	0.10
APACHE II score at day 1, mean (SD)	14.4 (5.9)	18.4 (7.2)	<0.001
SOFA score at day 1, mean (SD)	6.3 (3.2)	8.0 (3.8)	<0.001
Time between onset of 2009 H1N1 symptoms and hospital admission, days, mean (SD)	4.1 (2.6)	4.0 (2.5)	0.77
Quadrants infiltrated in chest X-ray at ICU admission, mean (SD)	2.4 (1.1)	3.0 (1.0)	<0.001
Co-infection at ICU admission, *n* (%)	41 (15.6)	31 (25.4)	0.03
Early oseltamivir treatment, *n* (%)	62 (23.6)	17 (13.9)	0.02
Oseltamivir regimen (300 mg/day) at ICU admission, *n* (%)	197 (74.9)	89 (73.0)	0.67
Co-morbidities, *n* (%)			
asthma	28 (10.6)	10 (8.2)	0.58
chronic obstructive pulmonary disease	52 (19.8)	20 (16.4)	0.48
cardiovascular disease	16 (6.1)	13 (10.7)	0.14
haematological disease	9 (3.4)	17 (13.9)	<0.001
pregnancy	13 (4.9)	7 (5.7)	0.80
obesity	103 (39.2)	54 (44.3)	0.36
diabetes mellitus	30 (11.4)	16 (13.1)	0.60
HIV infection	3 (1.1)	3 (2.5)	0.38
neuromuscular disease	10 (3.8)	5 (4.1)	0.98
Shock at ICU admission, *n* (%)	163 (62.0)	90 (73.8)	0.02
Prone ventilation, *n* (%)	52 (19.8)	40 (32.8)	<0.05

Table 5. Multivariate analysis (logistic regression) of the impact of early antiviral therapy on mortality in 385 adult ventilated patients with 2009 H1N1 virus infection

Variable	OR	95% CI	*P* value
Prone ventilation	2.75	1.45–5.23	0.001
Number of quadrants infiltrated in chest X-ray	1.70	1.28–2.25	0.001
APACHE II score (by point)	1.10	1.05–1.14	0.001
Early oseltamivir treatment	0.44	0.21–0.87	0.02

Discussion

Findings from this large, prospective, multicentre investigation suggest that early oseltamivir administration was associated with favourable outcomes among critically ill ventilated patients with 2009 H1N1 virus infection. Our results indicate that in this population, one additional life would be saved for every eight patients treated with oseltamivir within the first 2 days of the onset of influenza symptoms. In addition, early oseltamivir administration was associated with lower ICU mortality and consumption of ICU resources, resulting from the reduction in ICU LOS and in days under MV.

The current investigation features a number of novel strengths.[3–6,8,11,23–26] Our study enrolled 657 consecutive critically ill patients who were prospectively admitted in 148 hospitals. In contrast, the two previously published studies[8,26] of the impact of antiviral treatment in patients with 2009 H1N1 virus infection enrolled only a limited number of critically ill patients. Jain *et al.*[8] reported that the only independent variable significantly associated with a positive outcome was antiviral drug administration within 2 days of illness onset. However, of the 272 patients included, only 68 (25%) were admitted to an ICU and the mortality rate observed was very low (7%). Moreover, Domínguez-Cherit *et al.*[26] observed that patients who survived were more likely to have received treatment with neuraminidase inhibitors (OR=7.4) than patients who died.

The pathogenesis of influenza illness suggests that inhibiting viral replication rapidly after infection onset might reduce the duration and intensity of symptoms. Several studies seem to confirm this hypothesis.[27–30] Lee *et al.*[29] reported that critically ill patients presented active viral replication that continued beyond the first 2 days of illness. In 147 patients hospitalized with influenza A, the authors observed that oseltamivir therapy started on or before day 4 was independently associated with an accelerated decrease in the number of viral RNA copies. Kaiser *et al.*[31] analysed >3500 patients with influenza-like illness from 10 placebo-controlled, double-blind trials of oseltamivir treatment. Pooled data demonstrated that oseltamivir treatment reduced the incidence of lower respiratory tract

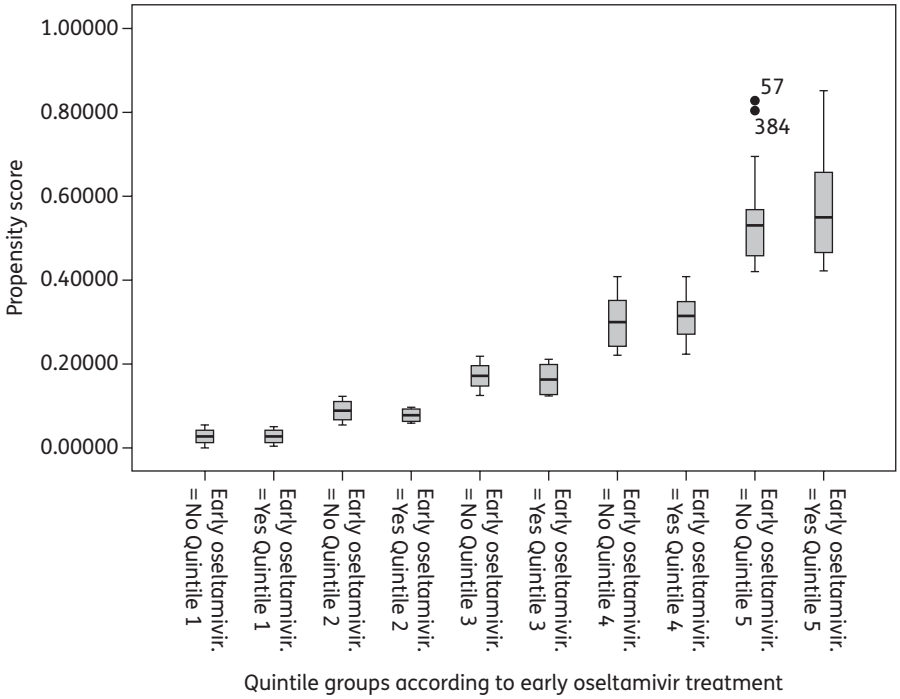

Figure 2. Distributions of the propensity scores for treated and untreated patients within each propensity score quintile were generally similar (with clear overlapping regions), reinforcing the validity of the propensity score analysis for early antiviral treatment.

complications, antibiotic use and hospitalization. Recently, Falagas *et al.*[12] evaluated the currently available published evidence on the impact of antiviral therapy on 2009 H1N1 infection. This review included >3000 patients with confirmed or probable 2009 H1N1 infection, but only 35% of them were critically ill. Despite some methodological limitations, the main conclusion was that administration of antiviral treatment with neuraminidase inhibitors within 2 days of symptoms onset was associated with a favourable outcome. Our findings corroborate this conclusion and provide clinical data confirming the impact of antiviral therapy on outcomes in a large cohort of critically ill patients.

Several studies have proved that viral clearance correlates with symptoms resolution and may be associated with shorter duration of hospitalization.[29,30] However, the correlation between promptness of antiviral administration and clinical resolution, manifested by a reduction in MV days, is unknown. In the current cohort, early antiviral administration was associated with a 3 day reduction in MV and a 7 day reduction in hospital stay, representing a significant reduction in resource utilization. The whole cohort received concomitant antibiotics, with no association between ET and number of antibiotic exposures. Co-infection was uncommon and its impact on outcomes has been reported elsewhere.[32]

Gastrointestinal absorptive function may be impaired in critically ill patients as a consequence of illness or shock.[33] In addition, underdosing is a common problem in patients with severe sepsis, MV with high distribution volume and low serum albumin.[34,35] These factors may decrease both half-life and peak concentration of antiviral drugs, and represent an important challenge in managing such patients. Some authors[36,37] have suggested maintaining high plasma trough concentrations or area under the curve values for oseltamivir at >50% of their maximal inhibitory concentration for influenza virus in order to achieve optimal suppression of viral replication. In our cohort, >70% of patients admitted to the ICU received a high dose of oseltamivir (300 mg/day) in accordance with WHO recommendations,[18] with the aim of achieving high concentrations; nevertheless, no differences in mortality rates between 150 and 300 mg/day regimens were found. These findings corroborate those of a recent study[38] of enteric absorption and pharmacokinetic patterns of oseltamivir in critically ill patients with 2009 H1N1 infection, which showed that the twice-daily standard dose of 75 mg obtained plasma levels similar to those in ambulatory patients and achieved maximum inhibition of the neuraminidase activity of the virus.

The present study has several potential limitations that should be addressed. First, it is an observational, non-interventional study, in which the participating ICUs from 148 hospitals were self-selected. Prescription of oseltamivir was chosen in accordance with local protocols. Although our study includes >70% of all patients admitted to the ICU during the present pandemic,[39] a selection bias cannot be ruled out. A prospective, controlled randomized clinical trial remains the optimal tool for demonstrating causality between treatment onset and mortality reduction. However, a study design of this kind would be difficult to implement at the present time. Propensity scores were calculated in order to reduce the potential bias in an observational study and to balance the baseline covariates observed in the treatment groups. Once estimated, propensity scores give a more accurate idea of the true treatment effect than a logistic regression model.[22] Second, only critically ill adults admitted to the ICUs

were included. There may be other unmeasured confounders, such as type of diabetes (I or II), diabetes control (HbA1C levels, organ damage), degree of chronic heart failure and severity of chronic obstructive pulmonary disease; therefore, our results may not be generalized to children or non-critically ill patients. Third, patients classified as 'late treated' may not have been recognized as influenza patients early enough. However, patients were classified according to time from onset of symptoms and not on the day of diagnosis. Finally, other authors have studied the impact of oseltamivir on clinical resolution patterns as primary endpoints. We did not investigate this point further, since the main goal of the present study was to assess the effect on ICU mortality in a cohort of critically ill patients.

In conclusion, our findings suggest that early oseltamivir administration increased survival among critically ill ventilated patients with 2009 H1N1 virus infection. Delay in antiviral administration has an appreciable effect on resource utilization by increasing length of ICU stay.

Acknowledgements

We are indebted to Michael Maudsley for linguistic assistance and David Suarez, PhD for statistical expertise.

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Funding

This study was supported in part by SEMICYUC (Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias), Instituto de Salud Carlos III: CIBERES (06/06/0036), and AGAUR 2009/SGR/1226.

Transparency declarations

None to declare.

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