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LETTER

Early oseltamivir therapy improves the outcome in critically ill patients with influenza: a propensity analysis

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Dear Editor,

Influenza affects between two and three million people worldwide each year, with complications responsible for a significant number of excess hospitalizations in intensive care units (ICUs) [1]. Since the newsworthy 2009 A(H1N1) pandemic (pdm), publications about influenza in ICUs remain scarce, with crucial outstanding issues on prognosis factors including the timing of antiviral treatments [2–5]. Here, we present a multicenter prospective study of critically ill influenza-infected patients aimed to identify prognosis factors associated with death.

This study was conducted from December 2008 to April 2013 in the 12 polyvalent ICUs from the Lyon catchment area (France). All adult patients admitted with microbiologically confirmed influenza infection were included. Following univariate comparisons, the independent contribution of patients' characteristics to in-hospital mortality was analyzed by backward stepwise multivariate analysis in a logistic regression model. Propensity score-matching was further used to compare similar patient populations receiving oseltamivir within or after 2 days of the onset of symptoms.

Over the study period, 201 patients were enrolled with the following main reasons for ICU admission: respiratory distress ($n = 174$, 87%), shock ($n = 13$, 6.5%), and neurological failure ($n = 7$, 3.5%). Infections were mostly caused by type A influenza virus ($n = 171$, 85%), with A(H1N1)pdm encountered in half of cases ($n = 100$, 50%). Other characteristics of the patients are presented in Table 1. Only 40 (20%) patients received antiviral treatment by oseltamivir within 2 days of the onset of symptoms. Day-28, ICU, and in-hospital mortalities were 18% (37/201), 21% (43/201), and 26% (53/201), respectively. Survivors were more likely to have received early oseltamivir therapy, with a significant trend in proportions of in-hospital mortality with increasing time from onset of symptoms to initiation of treatment ($p = 0.01$). Oseltamivir administration within 2 days of the onset of symptoms appeared as the sole independent determinant of a favorable outcome (OR 0.26; 95% CI 0.08–0.79, $p = 0.02$). After propensity score-matched analysis, oseltamivir therapy within 2 days of the onset of symptoms was associated with reduced in-hospital mortality (Supplementary Table 1).

The present study emphasizes the delay in oseltamivir administration as a major risk factor for in-hospital mortality. Influenza is a public health problem that, each year, causes both severe illness and deaths in high-risk populations [1]. With the exception of the 2009 pandemic, data on critical illnesses attributable to influenza are scarce. Thus, we designed the present study to provide current information on influenza disease in ICUs in the real situation of a specific territory. Concerning the severity of the patients' illness or the risk factors of death, our cohort is in agreement with previous studies on influenza-associated critical illness mainly drawn from 2009 pandemic studies [2, 3]. Nevertheless, our study does not confirm the negative impact on patients' outcomes of the influenza A(H1N1)pdm virus subtype. Importantly, as

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The list of co-investigators appears in the appendix at the end of the manuscript and in the ESM 2.

Table 1 Patients' characteristics according to outcome

	Total $n = 201$	Survivors $n = 148$	Non-survivors $n = 53$	Univariate analysis p	Multivariate analysis OR (95% CI)
Clinical features					
Age[a] (years)	63 ± 16	62 ± 15	66 ± 17	0.088	1.03 (1.00–1.05)*
Male sex	107 (53)	81 (55)	26 (49)	0.477	
Influenza vaccination	25 (12)	19 (13)	6 (11)	0.773	
BMI[a] (kg m^{-2})	27 ± 7	28 ± 7	26 ± 7	0.168	
No comorbidity	19 (9)	14 (9)	5 (9)	0.996	
SAPS II	44 ± 17	40 ± 15	54 ± 17	< 0.001	
Clinical course					
Symptom duration before ICU admission (days)	5.1 ± 5.0	5.1 ± 4.5	5.1 ± 6.0	0.931	
Influenza diagnosis before ICU admission	20 (10)	14 (9.5)	6 (11)	0.698	
Days from admission to influenza diagnosis[a]	2.3 ± 3.4	2.0 ± 2.7	2.9 ± 4.9	0.112	
Microbiological results					
Viral subtype				0.707	
Influenza A(H1N1)pdm[a]	100 (50)	73 (49)	27 (51)	–	
Other type A	71 (35)	54 (37)	17 (32)	–	
Type B	30 (15)	21 (14)	9 (17)	–	
Bacterial co-infection at admission	48 (24)	38 (26)	10 (19)	0.319	
VAP in the evolution[a]	51 (25)	31 (21)	20 (38)	0.016	1.91 (0.89–4.10)
Initial organ failures					
Type					
Respiratory	109 (54)	74 (50)	35 (66)	0.044	
Cardiovascular	86 (43)	58 (39)	28 (53)	0.003	
Neurological	50 (25)	30 (20)	20 (38)	0.011	
Hematological	24 (12)	8 (5.4)	16 (30)	< 0.001	
Renal	21 (10)	10 (6.8)	11 (21)	0.004	
Hepatic	2 (1.0)	1 (0.7)	1 (1.9)	0.459	
Number of failed organs	1.5 ± 1.2	1.2 ± 1.1	2.1 ± 1.2	< 0.001	
SOFA score[a]	6.6 ± 3.9	5.9 ± 3.8	8.7 ± 3.7	< 0.001	1.19 (1.08–1.30)*
Organ support during ICU stay					
Mechanical ventilation	179 (89)	126 (85)	53 (100)	0.003	
ARDS	113 (56)	73 (49)	40 (75)	0.001	
NIV only	36 (18)	31 (22)	5 (9.4)	0.061	
Days	14 ± 20	12 ± 17	19 ± 28	0.084	
ECMO[a]	8 (4.0)	4 (2.7)	4 (7.5)	0.211	
Catecholamines (days)	4.7 ± 8.8	3.3 ± 6.8	8.2 ± 12.4	0.005	
RRT (days)	3.9 ± 12.0	2.7 ± 8.8	7.3 ± 17.9	0.073	
Other treatments					
Prone position[a]	38 (19)	23 (15)	15 (28)	0.041	
Neuromuscular blockade	67 (33)	45 (30)	22 (42)	0.141	
Nitric oxide	19 (9.5)	11 (7.4)	8 (15)	0.101	

Table 1 continued

	Total $n = 201$	Survivors $n = 148$	Non-survivors $n = 53$	Univariate analysis p	Multivariate analysis OR (95% CI)
Oseltamivir	146 (73)	109 (74)	37 (70)	0.591	
Administration before ICU admission	17 (8.5)	13 (8.7)	4 (7.5)	0.999	
Dose (mg/day)	201 ± 84	197 ± 82	215 ± 98	0.257	
≤ 2 days after onset of symptoms[a]	40 (20)	36 (24)	4 (7.5)	0.009	0.26 (0.08–0.79)*
Days from onset of symptoms to initiation	4.9 ± 3.5	4.6 ± 3.6	5.7 ± 3.1	0.086	
Steroids[a]	91 (45)	63 (43)	28 (53)	0.288	

Data are number (%) or mean ± standard deviation, as appropriate

OR odds ratio, *CI* confidence interval, *BMI* Body Mass Index, *ICU* intensive care units, *VAP* Ventilator-Associated Pneumonia, *ARDS* Acute Respiratory Distress Syndrome, *SOFA* Sepsis-Related Organ Failure Assessment, *NIV* non–invasive ventilation, *ECMO* extra-corporeal membrane oxygenation, *RRT* renal replacement therapy

*$p < 0.05$

[a] Variables included in the backward stepwise logistic regression

confirmed by propensity analysis, oseltamivir administration was associated with better outcomes when administrated within 2 days of the onset of symptoms. This is the key message of our work, consistent with recent studies in non-severe forms of the disease, including meta-analysis of randomized clinical trials [4]. Indeed, the recent literature highlights the efficacy of oseltamivir to reduce the duration of symptoms, respiratory tract complications, and hospital admittance [4, 5]. Our results extend to the ICU setting the relationship between the delay of oseltamivir administration and the effectiveness of the treatment in patients with either A(H1N1)pdm or other influenza virus subtypes.

In conclusion, this real-life study emphasizes oseltamivir efficacy on in-hospital outcome when administrated within 2 days of the onset of symptoms. Even if physicians' awareness of the influenza disease has been undeniably enhanced since the last pandemic, many efforts are still required to improve influenza-infected patient management in ICUs, including early oseltamivir administration.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-017-4953-3) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

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Conflicts of interest
The authors declare they have no conflict of interest.

Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of our institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. For this type of study formal consent was not required.

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