Intensive Care Med (2015) 41:1365–1366
DOI 10.1007/s00134-015-3816-z

LETTER

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High-dose versus standard dose oseltamivir for treatment of severe influenza in adult intensive care unit patients

Accepted: 9 April 2015
Published online: 8 May 2015

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-015-3816-z) contains supplementary material, which is available to authorized users.

Dear Editor,

The Centers for Disease Control and Prevention (CDC) suggest that higher doses (i.e., 300 mg/day) of oseltamivir may be warranted in patients with severe influenza infection [1]. Two prospective, controlled trials have not demonstrated differences in clinical outcomes between patients treated with high-dose versus standard dose oseltamivir; however, only a small number of critically ill adults requiring intensive care unit (ICU) admission were included in these analyses [2, 3]. To provide additional insight into the optimal dosing of oseltamivir in patients with severe influenza, we conducted a retrospective cohort study to evaluate differences in clinical outcomes for 123 critically ill patients with influenza receiving high-dose or standard dose oseltamivir.

With Investigational Review Board approval, we collected demographic and treatment-related data on adult patients with laboratory-confirmed influenza who required ICU admission with supplemental oxygen above baseline and who were treated with oseltamivir for at least 24 h. Patients were divided into high-dose (>150 mg/day) or standard dose (≤150 mg/day) oseltamivir therapy based on renally adjusted daily dose (Table 2 in Supplementary Material). The primary objective was difference in ICU-free days. Secondary objectives included a comparison of the change in the Sequential Organ Failure Assessment (SOFA) score between 0 and 48 h after oseltamivir initiation (delta $SOFA_{0–48h}$), ventilator-free days, and 28-day mortality. For a full description of methods, please refer to the Supplementary Material.

As anticipated, differences in baseline characteristics were noted (Table 3 in Supplementary Material). Compared with the standard dose group ($n = 46$), patients in the high-dose group ($n = 77$) were younger (52.7 vs. 60.4 years; $p < 0.01$), had a higher median SOFA score on day 1 of therapy (7 vs. 5; $p = 0.02$), had a higher fraction (%) of inspired oxygen (FiO_2) on day 1 of therapy (75 ± 28 vs. 51 ± 24 %; $p < 0.01$), and were more commonly infected with influenza A (78 vs. 54 %; $p = 0.02$) . There were no differences in baseline comorbidities or in the use of vasoactive medications, antibiotics, corticosteroids, and other influenza antivirals between groups (Table 4 in Supplementary Material). Patients in the high-dose group had fewer ICU-free days than the standard dose group, fewer ventilator-free days, and a higher 28-day mortality rate (Table 1). There were no differences in other secondary outcomes, including hospital length of stay and time to return to baseline oxygen requirements. On multivariable analyses, high-dose therapy was not independently associated with time to ICU discharge [hazard ratio 1.35, 95 % confidence interval (CI) 0.81–2.27] or 28-day mortality (odds ratio 2.63, 95 % CI 0.93–7.55).

Table 1 Outcomes of intensive care unit patients treated with high-dose of standard dose oseltamivir

Variable	Standard dose oseltamivir ($n = 46$)	High-dose oseltamivir ($n = 77$)	p value
Intensive care unit-free (days)	16.5 (1.5–25.0)	2 (0–21.5)	0.015
Ventilator-free (days)	22 (7.5–28.0)	10 (0–25.0)	<0.01
Delta $SOFA_{0–48h}$[a]	1 (−1–2)	1 (−1–2)	0.43
28-Day mortality	7 (15.2)	30 (39.0)	<0.01
	Standard dose ($n = 39$)[b]	High-dose ($n = 47$)[b]	
Hospital length of stay (days)	20 ± 15	20 ± 18	0.88
Time back to pre-morbid O_2 requirements (days)	15 ± 14	18 ± 19	0.49

All data are reported as the mean ± standard deviaiton, or as the median with the interquartile range in parenthesis, as appropriate

[a] Sequential Organ Failure Assessment score between 0 and 48 h after initiation of oseltamivir therapy

[b] Assessment of these outcomes did not include patients who died before 28 days

The rationale for high-dose oseltamivir is supported by the notion that maintaining higher plasma concentrations of oseltamivir will result in a more substantial decrease in viral load. This has been demonstrated in mice, where oseltamivir produced a dose-dependent antiviral effect against the highly pathogenic avian H5N1 VN1203/04 influenza strain [4]. This dose-dependent effect may be most beneficial in patients with severe influenza pneumonia where viral loads are higher. In critically ill adults, however, average plasma concentrations of oseltamivir with a renally equivalent dosing regimen of 75 mg twice daily have been reported to be 2000- to 4000-fold higher than the 50 % maximal inhibitory concentration for H1N1 isolates, supporting the argument for standard dosing of oseltamivir [5]. Despite the CDC suggestion for the use of high-dose oseltamivir in severe influenza, these data do not support a clinical outcomes benefit with this dosing strategy in the critically ill.

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