

Sarah C. Welch Simon W. Lam Elizabeth A. Neuner Seth R. Bauer Stephanie N. Bass

## 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 © Springer-Verlag Berlin Heidelberg and ESICM 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<sub>0-48h</sub>), 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 highdose group (n = 77) were younger (52.7 vs. 60.4 years; p < 0.01), had ahigher median SOFA score on day 1 of therapy (7 vs. 5; p = 0.02), had a higher fraction (%) of inspired oxvgen (FiO<sub>2</sub>) on day 1 of therapy  $(75 \pm 28 \text{ vs. } 51 \pm 24 \%; p < 0.01),$ 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) Ventilator-free (days) Delta SOFA <sub>0-48h</sub> <sup>a</sup> 28-Day mortality	16.5 (1.5–25.0) 22 (7.5–28.0) 1 (–1–2) 7 (15.2) Standard dose $(n = 39)^b$	2 (0-21.5) 10 (0-25.0) 1 (-1-2) 30 (39.0) High-dose $(n = 47)^{b}$	0.015 <0.01 0.43 <0.01
Hospital length of stay (days) Time back to pre-morbid O <sub>2</sub> requirements (days)	Standard dose $(n = 39)$ $20 \pm 15$ $15 \pm 14$	Figh-dose $(n = 47)$ $20 \pm 18$ $18 \pm 19$	0.88 0.49

All data are reported as the mean  $\pm$  standard deviation, or as the

<sup>&</sup>lt;sup>b</sup> Assessment of these outcomes did not include patients who died before 28 days

median with the interquartile range in parenthesis, as appropriate <sup>a</sup> Sequential Organ Failure Assessment score between 0 and 48 h after initiation of oseltamivir therapy

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 2. 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 highdose oseltamivir in severe influenza,

these data do not support a clinical outcomes benefit with this dosing strategy in the critically ill.

## References

- 1. Prevention Centers for Disease Control and Prevention (2011) Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). Morb Mortal Wkly Rep 60:1–25
- 2. Lee N, Hui DS, Zuo Z, Ngai KL, Lui GC et al (2013) A prospective intervention study on higher-dose oseltamivir treatment in adults hospitalized with influenza a and B infections. Clin Infect Dis 57:1511–1519
- 3. South East Asia Infectious Disease Clinical Research Network (2013) Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial. BMJ 346:f3039

- Yen HL, Monto AS, Webster RG, Govorkova EA (2005) Virulence may determine the necessary duration and dosage of oseltamivir treatment for highly pathogenic A/Vietnam/1203/04 influenza virus in mice. J Infect Dis 192:665–672
- Ariano RE, Sitar DS, Zelenitsky SA, Zarychanski R, Pisipati A et al (2010) Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. CMAJ 182:357–363
- S. C. Welch (☑) · S. W. Lam · E. A. Neuner · S. R. Bauer · S. N. Bass Department of Pharmacy, Cleveland Clinic, 9500 Euclid Ave HB-105, Cleveland, OH 44195, USA e-mail: welchs@ccf.org