Did Oseltamivir Really Improve Survival in Critically Ill Patients With Influenza A (H1N1) pdm09?

TO THE EDITOR—I read with interest the recent article by Louie et al [1] that reported an impressive improvement in survival associated with neuraminidase inhibitor (oseltamivir) use in critically ill patients with influenza A (H1N1) pdm09 (pH1N1) infection. This article adds to a number of other observational studies that report a similar improvement in survival with oseltamivir in pH1N1 infection [2–4]. On the contrary, the efficacy of oseltamivir in preventing complications in patients with seasonal influenza is the subject of a heated controversy [5–7]. Although the authors put forth some biological rationale to explain the observed association, it is pertinent to ask the question whether the observed association was a real one.

First, there were important differences between the groups studied by Louie et al. Patients who were not treated with neuraminidase inhibitors had a significantly higher median age and more comorbidities such as diabetes, renal failure, and morbid obesity. It is likely that there were other characteristics that were not studied but influenced the chances of being treated with a neuraminidase inhibitor and survival. Possible confounders, such as immunization status, whether patients were treated early or late in the epidemic, and other sociodemographic factors, were not considered before ascribing a causal association with oseltamivir use. It is surprising that the authors did not perform a multivariable analysis to adjust for confounding despite having a large sample size.

Second, the authors interpret the data to mean that untreated patients had less severe disease. I disagree with this. Patients in the untreated group had a shorter hospital stay, probably due to the higher case fatality in this group. Paradoxically, the authors interpret this as an indication of less-severe disease. Untreated patients presented to the hospital earlier by 1 day, confirming the suspicion that they actually had more severe disease, yet they were less likely to be treated with neuraminidase inhibitors. These patients probably had some unapparent characteristic that adversely influenced the chances of being treated but was not studied. Even beyond the fifth day, survival of treated patients was consistently better, although it was not statistically significant owing to the small number of patients in each stratum. Thus, there is ample reason to believe that the 2 groups were not prognostically well balanced. Without addressing this prognostic imbalance, the authors attribute the difference to treatment effect.

Finally, the authors point out the fact that placebo-controlled trials to address this question would be challenging to undertake. To circumvent the ethical concerns, one strategy recommended by the US Food and Drug Administration is “a randomized and blinded dose-response (or duration-response) trial, in which a significant dose response is demonstrated” [8]. In the present study, 278 of 1671 (17%) patients were treated with a double dose of oseltamivir, and half of the patients were treated for more than the standard duration of 5 days (the median duration of antiviral treatment as reported was 5 days [range, 0–32 days]) [1]. One question that inevitably emerges is whether the double-dosing and longer treatment durations were associated with better survival.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Clinical Infectious Diseases 2013;56(7):1062
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DOI: 10.1093/cid/cis1212