

Has Oseltamivir Been Shown to Be Effective for Treatment of H5N1 Influenza?

Robert B. Couch¹ and Barry R. Davis²

¹Department of Molecular Virology and Microbiology, Baylor College of Medicine, and ²The University of Texas School of Public Health, Houston, Texas

(See the article by Adisasmito et al, on pages 1154–1160.)

Influenza A(H5N1) virus is one of many avian influenza viruses and was identified as the cause of 18 hospitalizations and 6 deaths in Hong Kong in 1997; the slaughter of 1.5 million poultry is credited with aborting the outbreak [1–3]. The concern that this event provoked for an occurrence of an H5N1 pandemic was reinforced when H5N1 infections were detected in 2003 in children in Vietnam; exposure to poultry was documented for 8 of 9 cases [4]. Expanded surveillance recorded H5N1 outbreaks in poultry throughout Asia and in other parts of the world [3, 5]. These occurrences in poultry led to recognition of H5N1 infections and disease in humans exposed to infected poultry, a circumstance that has continued to date [6].

Most H5N1 infections in humans result in a severe pneumonia with a high mortality rate, but with little ability to spread among humans [4, 6]. It is proposed that pneumonia is the characteristic H5N1 disease in humans because the avian influ-

enza virus receptor is prevalent on terminal bronchioles and lung alveolar cells, and not on the epithelial cells of the respiratory passages [7]. Unless the feared mutation(s) leading to a typical influenza virus infection of the respiratory passages occurs, H5N1 will likely remain primarily an uncommon severe pneumonia caused by exposure to infected poultry. Nevertheless, this threat of a change leading to a pandemic has caused an extensive worldwide effort to develop preventive vaccines [8, 9].

As of 1 June 2010, the World Health Organization (WHO) has documented 498 cases of H5N1-induced disease and 295 (59%) deaths [10]. The bulk of documented cases (79%) have been in Indonesia, Vietnam, and Egypt, with a mortality rate of 82%, 50%, and 31%, respectively. Clinical descriptions of H5N1 cases have indicated that the viral load is usually much higher than those seen in cases of H3N2 or H1N1 seasonal influenza, and is higher in fatal cases than in nonfatal cases; moreover, levels of several cytokines and chemokines were also higher among cases of H5N1 than in cases of H3N2 or H1N1, and among fatal cases than among nonfatal cases [11, 12]. Although cytokine dysregulation has been proposed for the so-called cytokine storm, it seems primarily attributable to a “viral load storm,” and the sequence of high viral load leading to high cytokine load frequently leads to de-

velopment of the acute respiratory distress syndrome, respiratory failure, and death. The fact that survivors of H5N1 influenza had lower levels of virus in secretions and that survival was associated with reducing titers with time of illness supports the notion that antiviral treatment should ameliorate severe disease and reduce the mortality risk.

Because of variable resistance to the M2 inhibitors, absence of an approved parenteral antiviral, and the requirement for inhalation for zanamivir activity, oseltamivir was recommended and has been used when possible for treatment; it was shown to be effective in vitro for suppression of H5N1 virus replication [13]. However, early experience with oseltamivir treatment did not suggest a substantial benefit, and a concern for resistance development emerged [4, 11, 12]. This initially discouraging circumstance was thought possibly to be attributable to late onset of treatment and altered pharmacokinetics because of illness severity and gastrointestinal symptoms. However, subsequent experience in larger numbers of patients suggested oseltamivir treatment could reduce the risk of death; earlier treatment conveyed enhanced patient survival in Indonesia, and treatment enhanced survival in Vietnamese patients [14, 15]. Additionally, an H5N1 update from WHO pooled the results of oseltamivir treatment from various countries

Received 15 June 2010; accepted 15 June 2010; electronically published 10 September 2010.

Potential conflicts of interest: none reported.

Reprints or correspondence: Dr Robert B. Couch, Department of Molecular Virology and Microbiology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030 (rcouch@bcm.edu).

The Journal of Infectious Diseases 2010;202(8):1149–1151

© 2010 by the Infectious Diseases Society of America. All rights reserved.

0022-1899/2010/20208-0001\$15.00

DOI: 10.1093/infdis/jiq261

and proposed an overall reduction in death of 74%, and a surprising reduction of 95% in countries with clade 2 infections [6]. Variation in virulence of different H5N1 viruses has been suggested as accounting for lower mortality in some locations, as has been seen in Egypt; a comparison of a Vietnamese strain and a Turkey strain in ferrets indicated the Vietnamese strain (a clade 1 strain) was more virulent than the Turkey strain (a clade 2 strain) [16].

In an effort to collect all information on avian influenza virus infections in humans, the F. Hoffman-LaRoche Company provided funding to Outcome Sciences, Inc, for developing an avian influenza infection registry [17]. The report on effectiveness of antiviral treatment of human influenza A(H5N1) infections by Adisasmito et al [18] in this issue of the *Journal* represents an analysis of data in the registry. Three hundred eight cases from 12 different countries were identified for analysis. Those treated with oseltamivir alone were compared with those not known to have been treated. Multivariate modeling showed a 49% reduction in mortality among those treated, with a significant reduction detected in all age groups and when drug therapy was started as late as 8 days after illness onset. These results are similar to those reported earlier for Indonesia and Vietnam but complemented those reports with larger numbers of cases from numerous locations in 12 different countries, involving different clades of H5N1 viruses, over a period of ~12 years. This comparison of data on treatment versus nontreatment represents a major departure from the data that would be available for such a comparison from a randomized controlled study. The quality of medical records, available data, and quality of medical care are likely to vary considerably. Controlling for uneven data and conducting a comparison free of bias and potential confounding variables are daunting tasks. In recent years, analytic methods have been developed to assess treatment effects in nonrandomized com-

parisons, such as that conducted of the multisite data on treatment of H5N1 influenza. These methods have value but also limitations. Consideration of their application to the registry data seems appropriate.

There are 2 major concerns of the analysis by Adisasmito et al [18]. First, there were a number of imputations of unobserved data for time to censoring, time to death, and time of treatment. The method of imputation used did not account for any variation; it assigned mean values of observed data when it would have been better if some form of multiple imputation had been used [19, 20]. However, even imputation in a randomized controlled trial can lead to bias. Second, the propensity score adjustment was used; to clarify, the propensity score is a patient's probability of being treated versus control as a function of all relevant observed covariates [21]. When the true propensity score is known, it provides an unbiased estimate of the effect of treatment versus control for patients with that propensity score. In a randomized controlled trial with half of patients receiving treatment and half receiving control, the propensity score for everyone is the same and comparing the 2 groups provides an unbiased estimate of treatment. On the other hand, if healthier patients are more likely to be treated, comparing the outcomes of treated and control patients would be biased; this bias can be corrected using propensity scores which permit comparison of treated and control patients with the same propensity value. In nonrandomized studies, propensity scores are not known; but, if treatment assignment can be assumed to be unconfounded, one can estimate the propensity scores using observed covariates to predict assignment using logistic regression. However, propensity scores can adjust only for observed covariates, whereas, in a randomized controlled trial, randomization balances for both known and unknown factors. Because of this limitation, confidence in conclusions using propensity scores in nonrandomized

studies needs to be additionally assessed for consistency of results with other evidence and for biological plausibility [22]. Thus, the conclusions on the value of oseltamivir treatment of H5N1 infections presented by Adisasmito et al [18] can be considered to be reasonable, based on other evidence and plausibility, but not definitive.

It is perhaps most reasonable to consider the current status of the recommended 5 days of treatment of H5N1 influenza in humans with standard dosages of oseltamivir as probably effective but in need of improvement. The major need for improvement, as emphasized in the present study, is the need for instituting treatment early in the course of infection, a fundamental tenet of treatment of an infectious disease. Animal model data on H5N1 infections suggested that both higher dosages and longer durations of treatment might be needed for H5N1 influenza [16, 23]. Fourteen cases in the Adisasmito report were treated with higher than standard dosages and 7 (50%) survived; 20 were treated for longer than 5 days (median, 7 days) and 15 (75%) survived. In view of the need for better treatment and the safety data available on higher dosages (150 mg twice daily) and longer durations of oseltamivir treatment, it seems reasonable to adopt the WHO proposed treatment of a higher dosage and duration of 10 days for H5N1 influenza and possibly all cases of influenza pneumonia [6]. Finally, parenteral treatment with either the unapproved peramivir or zanamivir preparations may be best for this severe disease [6].

In summary, the combined experience with oseltamivir treatment by Adisasmito et al [18] supports the belief that oseltamivir given orally at approved dosages for 5 days is beneficial for treatment of H5N1 influenza, particularly if treatment is started early in the course of illness. However, improvement in therapy is needed, and available data suggest oral therapy with a higher dosage (150 mg twice daily) and a longer duration (7–10

days) or parenteral therapy with peramivir or zanamivir are likely to improve on the standard oral oseltamivir treatment regimen.

References

1. Yuen KY, Chan PK, Peiris M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza. *Lancet* **1998**; 351:467–471.
2. Chan PK. Outbreak of avian influenza A(H5N1) virus infection in Hong Kong in 1997. *Clin Infect Dis* **2002**; 34(Suppl 2):S58–S64.
3. Peiris JSM, de Jong MD, Guan Y. Avian influenza virus (H5N1): a threat to human health. *Clin Microbiol Rev* **2007**; 20:243–267.
4. Hien TT, Liem NT, Dung NT, et al. Avian influenza A(H5N1) in 10 patients in Vietnam. *N Engl J Med* **2004**; 350:1179–1188.
5. Webster RG, Peiris M, Chen H, Guan Y. H5N1 outbreaks and enzootic influenza. *Emerg Infect Dis* **2006**; 12:3–8.
6. Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A(H5N1) Virus. Update on avian influenza A(H5N1) virus infection in humans. *N Engl J Med* **2008**; 358:261–273.
7. Shinya K, Ebina M, Yamada S, Ono M, Kasai N, Kawaoka Y. Influenza virus receptors in the human airway. *Nature* **2006**; 440:435–436.
8. World Health Organization. WHO consultation on priority public health interventions: executive summary (16–18 March 2004). http://www.who.int/csr/disease/avian_influenza/executivesummary/en/print.html. Accessed 27 April 2004.
9. Fauci AS. Pandemic influenza threat and preparedness. *Emerg Infect Dis* **2006**; 12:73–77.
10. World Health Organization. Cumulative number of confirmed human cases of Influenza A/ (H5N1) reported to WHO. http://www.who.int/csr/disease/avian_influenza/country/cases_table_2010_05_06/en/index.html. Published 6 May 2010. Accessed 1 June 2010.
11. de Jong MD, Thanh TT, Khanh TH, et al. Oseltamivir resistance during treatment of influenza A(H5N1) infection. *N Engl J Med* **2005**; 353:2667–2672.
12. de Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza A(H5N1) is associated with high viral load and hypercytokinemia. *Nature Med* **2006**; 12:1203–1207.
13. Hurt AC, Selleck P, Komadina N, Shaw R, Brown L, Barr IG. Susceptibility of highly pathogenic A(H5N1) avian influenza viruses to the neuraminidase inhibitors and adamantanes. *Antiviral Res* **2007**; 73:228–231.
14. Kandum N, Tresnaningsih E, Purba WH, et al. Factors associated with case fatality of human H5N1 virus infections in Indonesia: a case series. *Lancet* **2008**; 372:744–749.
15. Liem NT, Tung CV, Hien ND, et al. Clinical features of human influenza A(H5N1) infection in Vietnam: 2004–2006. *Clin Infect Dis* **2009**; 48:1639–1646.
16. Govorkova EA, Ilyushina NA, Boltz DA, Douglas A, Yilmaz N, Webster RG. Efficacy of oseltamivir therapy in ferrets inoculated with different clades of H5N1 influenza virus. *Antimicrob Agents Chemother* **2007**; 51:1414–1424.
17. Smith JR. Oseltamivir in human avian influenza infection. *J Antimicrob Chemother* **2010**; 65:ii25–ii33.
18. Adisasmito W, Chan PKS, Lee N, et al. Effectiveness of antiviral treatment in human influenza A(H5N1) infections: analysis of a global patient registry. *J Infect Dis* **2010**; 202(8):1154–1160 (in this issue).
19. Little RJA, Rubin DB. *Statistical analysis with missing data*. 2nd ed. Hoboken, New Jersey: John Wiley & Sons, **2002**.
20. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res* **2007**; 16:199–218.
21. Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized studies. *Stat Med* **2007**; 26:20–36.
22. Trojano M, Pellegrini F, Paolicelli D, Fuiani A, Di Renzo V. Observational Studies: Propensity Score Analysis of Non-randomized Data. *Int MS J* **2009**; 16:90–97.
23. Yen H-L, Monto AS, Webster RG, Govorkova EA. 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* **2005**; 192: 665–672.