Correspondence

Strengthening Observational Evidence for Antiviral Effectiveness in Influenza A (H5N1)

To the Editor—We recently reported findings from the largest ever patient registry of confirmed influenza A (H5N1) cases [1]. Using data collected from medical records, data made available by ministries of health and other clinical data sources, and data from published case reports, the registry deployed a structured data collection system to assemble data from 308 cases in 12 countries. The source documents for the registry contained varying types of information. The amount of missing data depends on both the record source, because not all data elements of interest were available from every source, and the reporter, because published case studies were selective in their reporting, and individual physicians had different styles and completeness of medical record annotations.

The study showed a strong reduction in the risk of mortality for treatment with oseltamivir. In the editorial that accompanied this first report of findings from the global registry of human H5N1 cases, Couch and Davis [2] commented on the challenges of controlling for uneven data and bias-free comparisons when using observational data. While affirming the overall conclusion that treatment with oseltamivir significantly reduces mortality when commenced even as late as 6–8 days after symptom onset, they questioned the methods used for handling missing data.

For one key analysis, we used Cox proportional hazards regression to estimate the hazard ratio for survival associated with oseltamivir treatment, and used a propensity score predicting probability of oseltamivir treatment for statistical adjustment in the Cox model. In the Cox model, we used mean imputation to estimate time from first presentation for medical care to death for 54 cases that were missing this information. For the propensity score, if time from symptom onset to first presentation for medical care was missing, it was dropped from the modeling step, but propensity scores were still generated for the 18 cases missing this date. A second key analysis examined survival by timing of oseltamivir initiation and used a complete case method, which resulted in exclusion of 61 cases missing dates of symptom onset, oseltamivir treatment start, presentation for medical care, and/or death.

To evaluate the sensitivity of our overall study conclusions to the data imputation method, we used multiple imputation of missing data and replicated the Cox proportional hazards model on 20 imputed data sets. The overall estimate of benefit was essentially unchanged, showing roughly a 50% decrease in the risk of death from treatment with oseltamivir. The confidence intervals in the Cox model were broader with use of multiple imputation than with use of mean imputation because mean imputation causes some artificial central grouping of values. For the analysis of survival by treatment timing, we also used multiple imputation methods to assign cases to treatment time intervals when some relevant dates were missing. This new approach allowed inclusion of a greater number of cases (n = 282) than in the original analyses (n = 221). The risk ratios obtained following multiple imputation were also very similar to those obtained in the original analysis, but with tighter 95% confidence intervals (Figure 1).

Thus, the findings reported from this observational study remain unchanged when more sophisticated multiple imputation techniques are employed to address the issue of missing data. The results obtained, which show the strong life-sparing benefit of oseltamivir even when administered late in the course of illness, illustrate the tremendous value of using a disease registry derived from collection of data in real-world clinical settings to study treatment effectiveness for a highly pathogenic, emerging infectious disease.

Funding

The registry is funded by a contract to Outcome Sciences from F. Hoffmann-La Roche. The sponsor provides scientific collaboration and has rights to nonbinding review of manuscripts but does not have the right to decide whether papers should be submitted for publication or to choose authors; nor does it have the right to approve wording of any manuscripts.

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Received 22 February 2011; accepted 7 April 2011.
Figure 1. Comparison of relative risk of survival by timing of oseltamivir initiation between complete case and multiple imputation analysis. Squares, complete case analysis; diamonds, multiple imputation analysis. CI, confidence interval.