The evidence of Oseltamivir (Tamiflu®) in reducing influenza mortality

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Send response to journal:

Re: The evidence of Oseltamivir (Tamiflu®) in reducing influenza mortality

The study: Nordstrom BL, Zhu S, Smith JR. Reduction of influenza complications following oseltamivir use [abstract]. Ingenix i3 Magnifi Epidemiology, Auburndale, MA and Hoffman-La Roche Ltd., Basel, Switzerland. ESWI 2005. Abstract 937.

The study population was derived from the Ingenix Research Data Mart (RDM), which contains information on over 20 million individuals from 1995 to the present. The database included data both from patients insured by United Healthcare and from large national employer groups with administrative services provided by United Healthcare. RDM includes medical claims data and pharmacy claims data. Using the RDM, patients of all ages during the period of November 1999 to March 2004 clinically diagnosed with influenza were identified and were grouped into two cohorts: those with a pharmacy dispensing of Tamiflu on the day of influenza diagnosis (N=39,202), and those with influenza diagnosis but no antiviral treatment during the influenza season (N=136,799). The total number of patients in the study was 176,001. The outcomes measured included incidences of claims diagnoses of pneumonia or myocardial infarction, or in-hospital deaths identified in claims. All outcomes were considered potentially influenza-related only if they occurred within 30 days after the influenza diagnosis. Cox proportional hazards models stratified into ten-year age blocks provided hazard ratio estimates for the Tamiflu-exposed group compared to the non-exposed cohort.

In the observational study of over 176,000 patients of all ages with influenza, the risk of death during the 4-week period after influenza diagnosis was 11-fold lower in the Tamiflu-exposed group (1 death in 39,202 patients [0.003%]) compared with the untreated group (56 deaths in 136,799 patients [0.041%]), with a hazard ratio of 0.09 (95% CI of 0.01, 0.65; p = 0.02). These statistically significant findings clearly show that Tamiflu use is associated with a reduced risk of death.

Critical appraisal:

As long as the full text of the study is not available our appraisal is limited to the following key questions:

1. What were the key selection (inclusion & exclusion) criteria? Inclusion criteria was the clinical diagnose „influenza“. We don’t

know if the diagnostic test was standardised or if laboratory tests have been used. How many cases of influenza-like illness have been included in both groups?

2. Were exposure & comparison groups similar at start of study except for study exposures? Especially in relation to gender mix, age, stage of disease, social background, ethnic origin, co-morbidity, but also vaccination rates and time of death (first, second, third or fourth week after diagnose).

3. What outcome measures were used? The outcomes measured included incidences of claims diagnoses of pneumonia or myocardial infarction, or in-hospital deaths identified in claims. All outcomes were considered potentially influenza-related only if they occurred within 30 days after the influenza diagnosis. As there was just 1 death in the intervention group, it would be interesting to find out more about the cause and time of death of this single case.

4. Was follow up time sufficiently long? A 4-week follow up seems very long. It would be interesting to calculate relative, absolute risks and number needed to treat using the numbers of death in the first, second, third or fourth week after diagnose.

5. What methodological effect has a single case in a cohort study? What would have happened if nobody of the 39,202 persons would have died in the 4-week follow up? Then Tamiflu® would be a magic bullet with a relative and absolute risk reduction of 100%.. Especially in cohort studies it is a real methodological problem to have low numbers, as low numbers are often linked to great variation of the results

6. Absolute risk reduction and number needed to treat (NNT) to avoid one death The absolute risk reduction = 0,041 – 0,003 = 0,038%. The NNT to avoid one death in the 4-week period after influenza diagnosis is 2.632.

7. Eminence versus evidence (1) After the publication of the Cochrane Report in the Lancet on January 19th Roche launched a media release which is representative for the ongoing discussion: “Roche fundamentally disagrees with the conclusions reached by the authors that oseltamivir should not be used for the treatment or prevention of seasonal influenza. The conclusion is at odds with the opinion of experts and regulatory authorities around the world.”

8. Economic evidence: (2) There is good economic evidence that the business with Tamiflu® in the year 2005 was very successful.

With Tamiflu® alone Roche earned one billion Euros in the year 2005.

(1)Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367. Published online. 19.01.2006. http://www.thelancet.com/journals/eop
Roche Media News. Statement – In response to paper by Jefferson et al., published in the Lancet, 19 January 2006, “Antivirals for influenza in healthy adults: systematic review”. Basel, 19 January 2006. www.roche.com/med-cor-2006-01-19 accessed 01.03.2006

(2)F. Hoffmann – La. Roche AG. Media release. Roche 2005: Record sales and operating profit. Basel, 01.02.2006. www.roche.com/mrar05e.pdf accessed 01.03.2006

Competing interests: None declared