REVIEW

Commentary on Cochrane review of neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

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Abstract

In recent years there has been much debate and controversy surrounding the efficacy and safety of neuraminidase inhibitors for influenza, in part because the data underlying certain efficacy claims were not available for independent scrutiny. In 2014, a Cochrane review was published, based exclusively on an almost complete set of clinical study reports and other regulatory documents. Clinical study reports can run to thousands of pages, providing an extensive amount of information on the planning, conduct and results of each trial. After a protracted campaign to obtain the reports, the manufacturers of the medications provided them unconditionally. The review authors subsequently published the underlying documents simultaneously with the Cochrane review, endorsing the concept of open science. In the following commentary, the background to and results of this review are summarized and put into clinical context.

Keywords: Clinical study reports, Influenza, Neuraminidase inhibitors, Reporting bias, Systematic review
Article published online: XXX

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The Cochrane review – 2006 to 2009: published evidence only

The publically available evidence base for neuraminidase inhibitors has changed dramatically over the past 8 years. This change has not come about through the results of new trials being published in peer-reviewed journals. Rather, information that was previously treated as confidential, such as evidence available only to regulators, became publically available. The change was set in motion by a Japanese paediatrician who, during the H1N1 outbreak of 2009, commented on the Cochrane review of neuraminidase inhibitors for adults published in 2006 [1]. Dr Keiji Hayashi questioned Cochrane's finding that oseltamivir reduces the risk of complications of influenza, pointing out that this conclusion was based on a manufacturer-authored, pooled analysis of manufacturer-sponsored randomized controlled trials, eight of which were unpublished [2] (to this day the eight trials remain unpublished). To address readers' comments, authors of Cochrane reviews are required to respond within 6 months, hence the neuraminidase inhibitors review authors set about obtaining the unpublished data. Initially, they were unsuccessful [3] and the data from the unpublished trials were not included in the updated 2009 version of the review [4].

The Cochrane review – 2009 to 2012: partial clinical study reports

In late 2009, the manufacturer of oseltamivir released part of the clinical study reports (CSRs) for all ten trials. CSRs are extensive documents reporting on clinical trials used to obtain regulatory approval [5]. Roche (Basel, Switzerland) did this in response to the 2009 Cochrane review of adults documenting that the majority of oseltamivir data had never been published and media reporting indicating that at least one major published

http://dx.doi.org/10.1016/j.cmi.2014.10.011

trial was ghost-written [7]. The partial CSRs that Roche provided were still insufficient to properly address Hayashi's comment. Further requests to the manufacturer were initially not fruitful and the Cochrane researchers turned to the European Medicines Agency (EMA), which introduced a policy of sharing CSRs with third parties in late 2010. During the process of obtaining oseltamivir CSRs from EMA, work on the 2012 version of the Cochrane review, which now included adults as well as children [6], was finalized, hence that review was only based on a subset of the relevant information (15 oseltamivir and ten zanamivir studies). In addition, the EMA had in its possession a full CSR for only one oseltamivir study. (EMA had no data on zanamivir.)

The Cochrane review – 2012 to 2014: full clinical study reports

In 2013, after a 4-year public campaign led by the *BMJ* (bmj.com/tamiflu), Roche unconditionally released full CSRs for all 77 sponsored clinical trials to the Cochrane group. The manufacturer of zanamivir (GlaxoSmithKlein; Brentford, UK) also provided a complete set of requested CSRs hence the 2014 version of the review [8] is based on the majority of relevant information although Japanese and Chinese studies of oseltamivir (three trials in total) are not included because of lack of complete CSRs.

The 2014 analysis included 46 randomized, placebo-controlled trials (20 of oseltamivir and 26 of zanamivir) on adults and children with confirmed or suspected exposure to naturally occurring influenza. Despite the title of the review including the words 'healthy adults', the elderly and patients with chronic diseases were included. The only population excluded comprised immunocompromised patients. All treatment trials recruited patients with influenza-like illness, defined as fever plus one constitutional symptom and one respiratory symptom. Influenza status was determined post-randomization using results from culture test and serology. Efficacy analyses in the Cochrane review were conducted on the intention-to-treat population of all randomized patients with influenza-like-illness, mimicking the situation of most clinicians in general practice, and safety analysis was based on all patients receiving at least one dose of study medication.

Results showed both oseltamivir and zanamivir have similar effects in terms of efficacy. Both medications reduce the time to first alleviation of symptoms of influenza-like illness in adults by around 10%. The reduction for oseltamivir was 0.70 days (95% CI −1.05 to −0.35 days, p <0.0001) whereas for zanamivir it was 0.60 days (95% CI −0.81 to −0.39 days, p <0.00001). There was no indication that the oseltamivir effect differed in subgroups of patients such as the elderly or those with chronic obstructive airways disease. However, because trials on these subgroups of patients were under enrolled, the manufacturer chose to combine the three trials in the elderly in a single clinical study report. The same occurred for the two trials in patients with chronic obstructive airways disease (Fig. 1). There was no evidence of a difference in treatment effect for zanamivir in the influenza-infected and non-influenza-infected subgroups (p = 0.53), suggesting that the effect of the neuraminidase inhibitors is not specific to influenza (Fig. 2). (Data were not available in a usable format to test this for oseltamivir.)

In children, the evidence is based on a small number of trials. For oseltamivir, time to first alleviation of symptoms was reduced in one trial of otherwise healthy children by 1.2 days (95% CI −1.9 to −0.49 days, p = 0.001) but not in three trials of children with asthma where patients in the oseltamivir groups took 0.2 days longer for initial alleviation of symptoms (95% CI −0.46 to 0.89 days, p = 0.53). There were only two trials of zanamivir in children with insufficient evidence of treatment

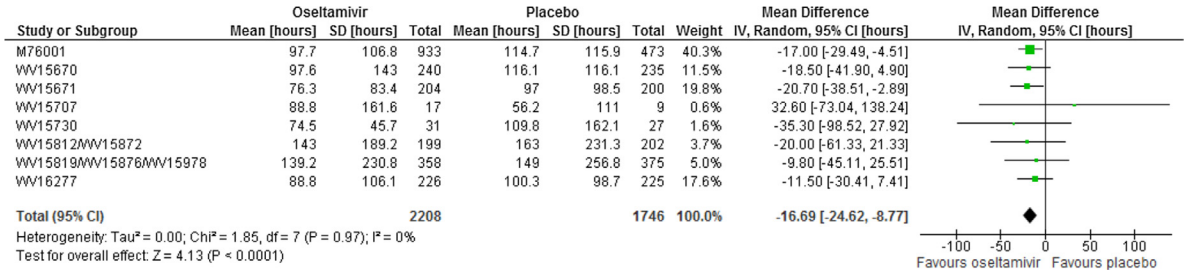

FIG. 1. Time (in hours) to first alleviation of symptoms in oseltamivir treatment trials of adults. (Please note that Study WV15812/WV15872 includes two under-recruited trials of patients with chronic obstructive airways disease that were combined by the manufacturer before reporting in the clinical study report and similarly Study WV15819/WV15876/WV15978 includes three under-recruited trials of the elderly that were combined by the manufacturer before reporting in the clinical study report. All other studies were in otherwise healthy adults.)

Please cite this article in press as: Jones M, et al., Commentary on Cochrane review of neuraminidase inhibitors for preventing and treating influenza in healthy adults and children, Clinical Microbiology and Infection (2014), http://dx.doi.org/10.1016/j.cmi.2014.10.011