Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data

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Pharmacy for its funding support ($10,000) for a study to analyse written medical information regarding the possible harms of statins. Peter Doshi is also an unpaid member of the IMEDS steering committee at the Reagan–Udall Foundation for the FDA, which focuses on drug safety research. CDelM is the Co-ordinating Editor of the Acute Respiratory Infections Group of the Cochrane Collaboration. CDelM reports personal fees from Key Pharmaceuticals during the conduct of the study; grants from the National Health and Medical Research Council (Australia), grants from NIHR (UK), personal fees from Elsevier and BMJ Books, from conference organisers for International Viral Infections Conference, personal fees from GlaxoSmithKline Pharmaceuticals, personal fees from Key Pharmaceutical, outside the submitted work. Rokuro Hama provided scientific opinions and expert testimony on 11 adverse reaction cases related to oseltamivir for the applications by their families for adverse reaction relief by the Pharmaceuticals and Medical Devices Agency (PMDA) and in the lawsuits for revocation of the PMDA's decision concerning with these reactions. Most of the cases were reported in the *International Journal of Research Studies in Management* (2008:**20**:5–36). Rokuro Hama was an expert witness in the lawsuit on the adverse reaction of (death from) gefitinib against AstraZeneca and Japanese Minister of Health Labour and Welfare, and provided scientific opinions and expert testimony. He argued that gefitinib's fatal toxicity was known before approval in Japan, as shown in 'Gefitinib story' (http://npojip.org/english/The-gefitinib-story.pdf) and in other articles (http://npojip.org/). Plaintiffs finally lost the case on 12 April 2013 at the Supreme Court of Japan. Rokuro Hama has received royalties from a published book.

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Scientific summary

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Scientific summary

Introduction

The World Health Organization (WHO) lists oseltamivir (Tamiflu®, Roche) as an essential influenza pandemic drug and worldwide there is considerable stockpiling for emergency use, but there is uncertainty on the reliability of the evidence base of oseltamivir and its fellow neuraminidase inhibitor (NI) zanamivir [Relenza®, GlaxoSmithKline (GSK)] and on their safety and efficacy.

In 2009 it emerged that there was substantial reporting bias in published evidence, and this led us to develop a new approach in order to update and amalgamate two pre-existing Cochrane reviews on NIs in children and adults. Over a period of 4 years we worked to obtain full, unabridged, clinical study reports for all trials in both drugs' evidence development programme. We based our current review and its 2012 predecessor uniquely on clinical study reports and other regulatory material, including regulators reports, that were available in the USA as Summary Basis of Approval and in the EU as European Public Assessment Report.

This undertaking was facilitated by the change of policy at the European Medicines Agency (EMA) in late 2010, allowing release for the first time of clinical study reports that were used during the Market Authorisation Application and its processing. Additionally, this process received the backing of the *British Medical Journal*, which launched its open data campaign on the basis of our quest for clinical study reports.

Here we present our methods and results, based on the full set of clinical study reports that fit our inclusion criteria. The reports, together with all relevant correspondence and the editors' and referees' comments, are also available. We also report our efforts to develop methods of reviewing clinical study reports and putting the trial evidence in the context of the numerous non-randomised studies that have been published since the 2009 influenza outbreak in order to present a complete picture of the topic.

Objectives

Our objective was to assess the effects of the NIs zanamivir and oseltamivir for influenza on the basis of regulatory material and within their context of use. Specifically, we aimed to:

1. describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all clinical study reports of published and unpublished randomised, placebo-controlled trials and regulatory comments
2. determine the effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza.

Methods

To evaluate the effectiveness of NIs for preventing and treating influenza in adults and children:

- We searched trial registries, electronic databases (to 22 July 2013) and regulatory archives, and corresponded with manufacturers to identify all trials. We also requested clinical study reports. We focused on the primary data sources of manufacturers but we checked that there were no published randomised controlled trials (RCTs) from non-manufacturer sources by running electronic searches in the following databases: the Cochrane Central Register of Controlled Trials, MEDLINE, MEDLINE (via Ovid), EMBASE, EMBASE.com, PubMed (not MEDLINE), the Database of Abstracts of Reviews of Effects, the NHS Economic Evaluation Database and the Health Economic Evaluations Database.
- We included evidence from RCTs testing the effects of NIs for prophylaxis, post-exposure prophylaxis and treatment of influenza.
- We included only trials on people who were exposed to naturally occurring influenza, with or without symptoms.
- We analysed the effects of zanamivir and oseltamivir on time to first alleviation of symptoms, influenza outcomes, complications, hospitalisations and adverse events in the intention-to-treat population.
- The sizeable quantity of available data led us to subdivide the extraction, appraisal and analysis of the data into a two-stage exercise. In stage 1 we assessed the reliability and completeness of the identified trial data. We decided to include in stage 2 of the review (full analysis following standard Cochrane methods) only data that satisfied the following three criteria: (1) completeness, (2) internal consistency and (3) external consistency.
- We used regulatory information to assess the possible correlation between citation frequency of oseltamivir treatment trials in the US Food and Drug Administration regulatory documents and trial size.
- We used the random-effects approach of DerSimonian and Laird (DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88), based on mean differences with 95% confidence interval (CI) for analysis of time to first alleviation of symptoms. For all other outcomes we used the random-effects approach for binary data of DerSimonian and Laird, where tau-squared was estimated using the inverse variance method.

To determine the effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza:

- We searched MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature, Web of Science and the Latin American and Caribbean Health Sciences Literature databases (see *Appendix 16* for details of our search strategy) for observational studies. We also hand-searched bibliographies from two relevant documents published by the WHO and two previous reviews.
- We included any study of patients with 2009A/H1N1 influenza reporting mortality outcomes and exposure to oseltamivir with at least 5% of patients untreated with influenza antiviral drugs and five or more deaths overall.
- We requested individual patient data (IPD) from the corresponding authors of all included studies and kept a record of all correspondence that ensued. IPD was provided for four studies, sent via e-mail in Excel® 2010 (Microsoft Corporation, Redmond, WA, USA) or Stata 12 files (StataCorp LP, College Station, TX, USA), checked for consistency and analysed in SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Effectiveness of neuraminidase inhibitors in the treatment of influenza

We obtained 107 clinical study reports from the EMA, GSK and Roche. We included 53 trials in stage 1 and 46 in stage 2, including 20 oseltamivir (9623 participants) and 26 zanamivir trials (14,628 participants). Most of the zanamivir studies and half of the oseltamivir studies were at high risk of selection bias as a result of inadequate reporting.

In adult treatment, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% CI 8.4 to 25.1 hours; $p < 0.0001$). There was no effect in asthmatic children, for whom symptoms increased by 5.2 hours (11.1 hours lower to 21.4 hours higher), but in otherwise healthy children there was reduction by 29 hours (95% CI 12 to 47 hours; $p = 0.001$). Zanamivir reduced the time to first alleviation of symptoms in adults by 0.60 days (95% CI 0.39 to 0.81 days; $p < 0.00001$) but the effect in children was not significant. In subgroup analysis there was no difference in treatment effect for zanamivir on time to first alleviation of symptoms in adults in the influenza-infected and non-influenza-infected subgroups ($p = 0.53$).

Oseltamivir significantly reduced unverified pneumonia [risk difference (RD) 1.00%, 95% CI 0.22% to 1.49%] in the treated population. The effect was not significant in the five trials that used a more detailed diagnostic form for pneumonia. There was no significant effect on pneumonia in children [risk ratio (RR) 1.06, 95% CI 0.62 to 1.83]. There was no significant effect of zanamivir treatment on pneumonia (RR 0.90, 95% CI 0.58 to 1.40). In two zanamivir adult trials, pneumonia reporting was based on a stricter definition of X-ray confirmation and there was also no significant treatment effect (RR 1.02, 95% CI 0.35 to 3.02). In prophylaxis, zanamivir significantly reduced the risk of unverified pneumonia in adults (RD 0.32%, 95% CI 0.09% to 0.41%) but not oseltamivir.

In adult treatment, oseltamivir increased the risk of nausea (RD 3.66%, 95% CI 0.90% to 7.39%) and vomiting (RD 4.56%, 95% CI 2.39% to 7.58%). The proportion of participants with fourfold increases in antibody titre was significantly lower with oseltamivir (RR 0.92, 95% CI 0.86 to 0.97). Oseltamivir significantly decreased the risk of diarrhoea (RD 2.33%, 95% CI 0.14% to 3.81%) and cardiac events (RD 0.68%, 95% CI 0.04% to 1.0%) during the on-treatment period. The rate of psychiatric adverse events increased in dose-dependent fashion based on a likelihood ratio test ($p = 0.038$) in the two 'pivotal' treatment trials that included two oseltamivir arms with doses of 150 mg and 300 mg daily. There was no indiction of a dose–response effect of treatment on psychiatric adverse events in the only prophylaxis study with multiple dose treatment groups. In the treatment of children, oseltamivir induced vomiting (RD 5.34%, 95% CI 1.75% to 10.29%). There was a significantly lower proportion of children on oseltamivir with a fourfold increase in antibodies (RR 0.90, 95% CI 0.80 to 1.00).

Effectiveness of neuraminidase inhibitors in the prevention of influenza

In prophylaxis trials, NIs reduced the risk of symptomatic influenza in individuals (oseltamivir RD 3.05%, 95% CI 1.83% to 3.88%; zanamivir RD 1.98%, 95% CI 0.98% to 2.54%) and in households (oseltamivir RD 13.6%, 95% CI 9.52% to 15.47%; zanamivir RD 14.84%, 95% CI 12.18% to 16.55%). There was no significant effect on asymptomatic influenza (oseltamivir RR 1.14 95%, CI 0.39 to 3.33; zanamivir RR 0.97, 95% CI 0.76 to 1.24). In oseltamivir prophylaxis, psychiatric adverse events were increased in the combined on- and off-treatment periods (RD 1.06%, 95% CI 0.07% to 2.76%). Oseltamivir, on treatment, increased the risk of headaches (RD 3.15%, 95% CI 0.88% to 5.78%), renal events (RD 0.67%, 95% CI –0.01% to 2.93%) and nausea (RD 4.15%, 95% CI 0.86% to 9.51%).

Comparison of core reports compared with full clinical study reports

With more detailed information, no previous assessment of 'high' risk of bias was reclassified as 'low' or 'unclear' in the main analysis, and over half (55%, 34/62) of previous assessments of 'low' risk of bias were reclassified as 'high'. Most 'unclear' risk of bias (67%, 28/42) was reclassified as 'high' risk of bias when our judgements were based on full clinical study reports.

Effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza

A total of 154 full-text articles were assessed for eligibility. Of these, 30 observational studies were eligible and a total of 11,013 patients were available for qualitative synthesis. Overall, there were 1301 deaths (12%) with the percentage of deaths receiving oseltamivir similar to that of survivors (83% vs. 82%). The IPD came from four studies including 3071 patients and 242 (8%) deaths. Analysis of the IPD showed no evidence of reduced risk of mortality with oseltamivir [hazard ratio (HR) 1.03, 95% CI 0.64 to 1.65].

Discussion

Effectiveness of neuraminidase inhibitors in the prevention and treatment of influenza

The evidence that we have presented and synthesised shows that both NIs have symptom-relieving effects, especially for self-reported outcomes, shortening symptom duration and reducing the frequency of symptoms such as cough. For oseltamivir, this effect perhaps extends to cardiac symptoms, despite the short duration of treatment (5 days). We are unsure what to make of this finding but we think it deserves further investigation.

We could not decide the level of diagnostic ascertainment of diagnosis of pneumonia and other complications. In a metaregression of all 32 included studies that reported on 'pneumonia', we found evidence that treatment effects for pneumonia are statistically different depending on the method of diagnosis.

Antibody suppression seems stronger for oseltamivir than zanamivir, probably because of the difference in bioavailability. It may be that evidence of other effects, such as hyperglycaemia and renal impairment (although significance was marginal) in the prophylaxis trials may be due to inhibition of the host's endogenous neuraminidase, which impairs the cell function of various organs.

A weak dose-dependent association between oseltamivir and psychiatric harms is evident in the two pivotal treatment trials (but not in all oseltamivir treatment trials combined). It is possible that influenza-like illness and influenza symptoms masked the harms in those who were already symptomatic and therefore recruited in the treatment trials (and influenza-type symptoms were excluded as adverse events to be reported).

Comparison of core reports compared with full clinical study reports

The Cochrane risk-of-bias tool was sometimes difficult to apply to clinical study reports. This may be because the tool was constructed to assess journal publications and comprises a checklist. As information increased in the core reports, our assessment of bias became more detailed and changed some of our assessments. Our experience suggests that a more detailed extraction sheet is needed to prompt reviewers to consider additional aspects of the study design when assessing bias.

Effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza

Analysis of the summary data on the 30 studies as well as the IPD showed evidence of time-dependent bias, with bias increasing with increasing odds of treatment. Analysis of the IPD using standard Cox regression on the 2056 patients with survival times gave a HR of 0.75. However, when the time-dependent nature of oseltamivir exposure, as well as the competing risk of hospital discharge were taken into account, the HR adjusting for potential confounding variables was 1.03.

Our results are substantially different from those of three other reviews, which based their primary analysis of mortality on three small studies of 681 patients, none of which had 2009A/H1N1, did not consider time-dependent treatment exposure or appeared to not take appropriate account of time-dependent treatment exposure.

Conclusions

Oseltamivir and zanamivir cause small reductions in the time to alleviation of influenza symptoms except for asthmatic children. The use of oseltamivir increases the risk of nausea, vomiting, psychiatric events in adults and vomiting in children. Observational studies do not show that oseltamivir has a protective effect on patients with 2009A/H1N1 influenza for mortality. Evidence suggests that the risk of bias has been insufficiently reported in other Cochrane reviews that are limited to published research. The balance between benefits and harms should be considered when making decisions about the use of NIs for either prophylaxis or treatment of influenza.

Research priorities

We could not reach a consensus on whether or not further trials are warranted and whether or not current trials should be discontinued. Any future trial designs should ensure that the presence of complications is ascertained using objective diagnostic criteria. Procedures for trial unblinding and dates of unblinding should be routinely reported. Registration should be made compulsory for all studies in which human beings are randomly assigned to experimental arms. There is a further need to develop the systematic review methods for the evaluation of other drugs, using full clinical study reports. Priority could perhaps be given to first drugs of a new family, drugs considered to be innovative or those that are likely to have a big market impact. Such reviews should be publicly funded, and independent from both regulators and manufacturers. To determine the risks and benefits of drugs there will be a need to move to more comprehensive reviews that incorporate more clinical study report data.

Study registration

This study is registered as PROSPERO CRD42012002245.

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