Systematic review with meta analysis

Zanamivir for influenza in adults and children shows limited benefit for treatment of symptomatic influenza and no effect on relevant complications

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Commentary on: Heneghan CJ, Onakpoya I, Thompson M, *et al.* Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ* 2014;348:g2547.

Context

The neuraminidase inhibitor zanamivir, administered as an inhaled powder, is approved for the prevention and treatment of influenza in adults and children older than 7 years. Previous systematic reviews (SRs) of zanamivir may have been affected by publication bias and missing data, and clinical recommendations based on such studies should be considered inadequate.[1 2] To deal with these shortcomings, this SR and meta-analysis (an update of a Cochrane Review)[3] reanalysed the prophylactic and treatment effects of zanamivir on those suffering from influenza, based on the full clinical study reports of all relevant trials provided by the manufacturer and on regulatory comments.

Methods

This review included randomised controlled trials (RCTs) testing zanamivir compared with placebo for prophylaxis, postexposure prophylaxis (PEP) and treatment of naturally occurring influenza with or without symptoms in healthy or chronically ill adults and children. Only intention-to-treat and safety populations were considered.

Primary outcomes were: (1) symptom relief, admission to hospital and complications for treatment trials, and (2) laboratory-confirmed influenza (symptomatic or asymptomatic), influenza-like illness admission to hospital and complications, interruption of transmission and harms for prophylactic trials.

The review adhered to recognised Cochrane Collaboration protocols for SRs and meta-analyses, and applied the risk-of-bias tool, complemented with new bias sources, to assess the quality of the clinical study reports. The results are reported as relative risk, risk difference (binary outcome data) and mean difference (continuous outcome data).

Findings

Twenty-eight RCTs met the inclusion criteria, reporting on 14 628 participants (7678 in treatment trials (N=20) and 6950 in prophylaxis trials (N=8)), with ages ranging from 5 to >65. Twenty-six trials fulfilled predefined criteria of completeness, internal consistency and external consistency.

Zanamivir reduced the time to first alleviation of symptoms in adults by 0.6 days (95% CI 0.39 to 0.81) from 6.6 to 6 days, but caused no reduction in children. Zanamivir did not reduce the risk on pneumonia, otitis media or sinusitis in adults and children. Only a small effect was noticed on bronchitis in adults (1.8%, 95% CI 0.65% to 2.80%), but not in children. No data were available to assess the effect on admissions. The prophylactic effect on symptomatic influenza was significant for individuals (1.98%, 95% CI 0.98% to 2.54%; number needed to treat to benefit (NNTB)=51, 95% CI 40 to 103) and households (PEP) with (14.84%, 95% CI 12.18% to 16.55%; NNTB=7, 95% CI 6 to 9). No significant reduction was noticed on asymptomatic influenza cases in individuals and households. Prophylaxis in adults reduced unverified pneumonia by 0.32% (95% CI 0.09% to 0.41%; NNTB=311, 95% CI 244 to 1086). No prophylactic effect could be seen on pneumonia in children or on bronchitis or sinusitis in adults and children. Zanamivir tended to be well tolerated (except for bronchospasm).

Commentary

Zanamivir can significantly increase the rate of symptom relief in adults with influenza. This finding confirms previous estimates and is comparable with observed effects of oseltamivir.[2 4] No treatment effect was seen on pneumonia. Prophylactic use only reduced symptomatic influenza or unverified pneumonia by a small amount. No evidence is provided on reducing the risk of transmission of the virus. Other preventive measures, such as vaccination or virus-barrier methods, are preferable.

The diagnostic criteria for clinical outcomes used in the trials were not always clear and uniform and were essentially based on self-reported symptoms. The small benefit of zanamivir does not exceed that of symptom relief drugs. This SR analysed, for the first time, the effect of the use of relief drugs, and showed that time to first alleviation of symptoms was shorter in all participants when any relief drugs were allowed compared with no use. Most trials were performed in healthy adults, not the elderly or those at high risk of influenza complications, which limits extrapolation to these vulnerable people.

The reviewers justified their new search methodology, based on an extensive analysis of clinical study reports, by citing the serious gaps they found in the published material (less than half the 28 RCTs) and the difficulty in retrieving unpublished data by conventional search methods. The evaluation of the quality of the reporting and the conduct of the trials identified many possible sources of bias.

New clinical trials on the effect of zanamivir are not warranted as new results are not expected to change the existing evidence. New SRs using previously published data will be biased beforehand and should be avoided, meaning that only those that use the thorough methodology of this Cochrane Review will be of interest.

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

References

1. **Jefferson T**, Jones MA, Doshi P, *et al.* Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012;1:CD008965.
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4. **Jefferson T**, Jones M, Doshi P, *et al.* Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ* 2014;348:g2545.