COCHRANE COLUMN

Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

JS Nguyen-Van-Tam[1]* and KG Nicholson[2]

1. Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK
2. Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK

(*corresponding author: jvt@nottingham.ac.uk)

Antivirals represent a rational approach to the management of influenza, but prior to approval of the neuraminidase inhibitors (NIs), zanamivir and oseltamivir, in 1999, only the M2-inhibitors, amantadine and rimantadine, were available, with limitations of rapid emergence of resistance, lack of activity against influenza B, and adverse central nervous system events. Oseltamivir is effectively the only antiviral widely available to manage influenza because administration of zanamivir by inhalation restricts its utility. NIs are used widely in Japan to treat seasonal influenza, but more cautiously elsewhere, driven by uncertainties about clinical benefit.

In 2005, a large international hearing co-hosted by WHO, FAO, OIE, and the World Bank noted the severity of avian A(H5N1) influenza (53.4% case fatality during 2003-05) and its considerable pandemic potential. Remarking on limited clinical data on NIs for treatment of human infection with H5N1, resistance of circulating strains to M2-inhibitors, challenges over vaccine procurement, and limited production capacity for NIs, members of the hearing recommended expansion of the global antiviral stockpile.[1] Contrary to expectation, the following pandemic in 2009 was caused by an A(H1N1) virus and killed ~284 500 people,[2] many fewer than pandemics of 1918, 1957, and 1968, prompting questions about the rationale of stockpiling neuraminidase inhibitors. So, does the updated Cochrane Review[3] provide incontrovertible evidence to justify or dismiss NIs for treating influenza?

The short answer is no. Altogether 107 reports were available but only 46 (20 oseltamivir, 26 zanamivir) were subjected to meta-analysis. The authors concluded that oseltamivir reduced time to alleviation of symptoms of influenza-like illness modestly, in adults and children by 16.8 and 29 hours respectively – confirming efficacy against trial endpoints. Oseltamivir had no significant effects on pneumonia, serious complications, hospitalisations or deaths, leading the authors to conclude, "treatment trials do not settle the question whether the complications of influenza (such as pneumonia) are reduced, because of a lack of definitions".[3] However, they acknowledge that included trials were mainly conducted in community settings against "relatively benign influenza"[2] [seasonal influenza] and there were "problems in the design of many of the studies that were included".[3] Simply put, the individual trials were not designed or powered to assess impact on severe illness or hospitalisations (Table 1), or deaths; the latter did not occur in any oseltamivir study.

Table 1: Examples of subject numbers included for analyses pertaining to oseltamivir[3]

Patient group	Outcome	Number*
Adults	Hospital admission	4394
Children	Hospital admission	1359
All ages	Pneumonia	4452
	Serious complications	3675

**total of subjects with influenza-like illness assigned to active treatment or placebo: Influenza confirmed in ~64% of adults and ~53% of children.*

Data on adverse events are more extensive and reassuring than in the last Cochrane review. Altogether, gastrointestinal events occurred in 24.0% of adults and 23.1% of children during the on-treatment period for influenza-like illness as compared with 17.8% (RR 1.25, 95%CI 1.08-1.45) and 19.5% (RR 1.18, 95%CI 0.96-1.44) respectively with placebo. Withdrawals due to adverse events and occurrence of psychiatric manifestations were similar with oseltamivir or placebo.[3] Intriguingly, oseltamivir significantly decreased the risk of undefined cardiac events compared to placebo during the on-treatment period (risk difference 0.68%, 95% CI 0.04 to 1.0), suggesting a plausible benefit of treatment.[3]

Clearly, efficacy data from the latest Cochrane Review cannot be applied confidently to formulate treatment policy or guidance for the management of patients hospitalised with seasonal influenza, especially those with life-threatening disease. The same applies to pandemic planning and stockpiling of antivirals. In these settings, which contrast to those in the Cochrane Review, policy-makers can draw on evidence from observational studies, accepting that they are more prone to bias. Nevertheless a substantial body of evidence suggests that NIs reduce complications and mortality in patients with severe influenza.[4-6] The evidence is especially strong from the 2009 pandemic period where a very large individual participant data (IPD) analysis based on 29 234 hospitalised subjects, of whom 86% had laboratory confirmed A(H1N1)pdm09, has recently demonstrated that mortality was reduced by one fifth overall, and by one half if treatment was started within 48 hours of illness onset.[7]

Taken together, the latest Cochrane Review findings (on treatment and prophylaxis) and those of recent observational studies (on complications and mortality) are not in conflict, but point to oseltamivir being an essential part of our defence against influenza.

Between October, 2007, and September, 2010, JSN-V-T undertook ad hoc paid consultancy and lecturing for influenza vaccine manufacturers (Sanofi Pasteur MSD, Sanofi Pasteur, GlaxoSmithKline, Baxter, Solvay, and Novartis) and manufacturers of neuraminidase inhibitors (F Hoff mann-La Roche, oseltamivir; and GlaxoSmithKline, zanamivir); he is in receipt of current or recent research funding related to influenza vaccination from GlaxoSmithKline and AstraZeneca and non-fi nancial support (travel) from Baxter, and his group received an unrestricted educational grant for research in the area of pandemic influenza from F Hoffman La-Roche used to fund the work by Muthuri and colleagues cited in the Commentary. . KGN was a founding member of the European Scientific Working Group on Influenza and resigned in 2001; within the past 5 years he received H5 vaccines from Novartis for MRC-funded research and H1N1 pandemic vaccines from GlaxoSmithKline and Baxter for NIHR-funded research.

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