Antivirals for influenza: where now for clinical practice and pandemic preparedness?

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Amid intense media coverage, the Cochrane Collaboration this month published an updated systematic review on the efficacy of neuraminidase inhibitors (NAIs) for influenza.[1] The authors identified 107 clinical study reports (CSRs) of published and unpublished randomized clinical trials (RCTs). Of these, less than half were included in the meta-analysis, which concluded that in adults oseltamivir reduced time to first alleviation of symptoms of influenza-like illness by 16·8 hours (95% confidence interval (CI) 8·4–25·1 hours, P<0·0001). In otherwise healthy children oseltamivir reduced illness by 29 hours (95% CI 12–47, P=0·001), but benefit was not evident in asthmatic children. Zanamivir cut symptom duration in adults by 0·60 days (CI 0·39–0·81), P<0·00001), but it had no significant effect in children. For serious influenza-related complications or those leading to study withdrawal, and radiologically-verified pneumonia, the available data did not reveal significant effects with either drug. There were no influenza-related deaths in the oseltamivir treatment trials and only two in the zanamivir treatment trials, as would be expected in community-based studies during seasonal outbreaks of influenza. Most patients in the included treatment studies were not at high risk of severe complications and the primary outcome in the vast majority of studies was time to alleviation of illness rather than morbidity and mortality outcomes relevant to pandemics or people with co-morbidities.

Despite incorporating extensive data from hitherto inaccessible CSRs, the new findings are little different from the first Cochrane review reported in 2000.[2] The included trials were not designed to assess impact on life-threatening complications, and absence of a reliable signal from such underpowered RCTs does not imply absence of effect. Nonetheless, the authors conclude, …"The treatment trials with oseltamivir or zanamivir do not settle the question of whether the complications of influenza (such as pneumonia) are reduced." We agree, as the included RCTs were

not appropriately designed or powered to assess impact on life-threatening complications. So, what are the implications of the review and of observational studies of NAIs in normal clinical practice? Are the Cochrane authors correct in stating “there appears to be no evidence for patients, clinicians or policy-makers to use these drugs to prevent serious outcomes, both in annual influenza and pandemic influenza outbreaks”?

In March 2014, a meta-analysis of observational Individual Participant Data (IPD) for 29,234 patients hospitalised with A(H1N1)pdm09 virus infection worldwide reported a roughly one-fifth (OR=0·81 (95% CI 0·70–0·93)) reduction in mortality associated with NAI treatment compared to no treatment, irrespective of the timing of starting treatment; and a halving of the risk of death (OR=0·50, 95% CI 0·37–0·67, P<0·001) if treatment was started within 48 hours of symptom onset.[3] These data from *hospitalised* patients during the 2009 A(H1N1) pandemic confirm the findings of multiple smaller observational studies of NAI treatment of hospitalized patients with seasonal, pandemic, or novel influenza A virus infections that have reported reductions in the risk of critical illness and death.[4-7] These associations with reduced mortality risk were less pronounced and not significant in children,[3] although other researchers have demonstrated significant reductions in mortality in children.[8] Given that the 2009 A(H1N1) pandemic produced more than 200,000 respiratory-related deaths worldwide,[9,10] the findings imply that many deaths were (and could have been) averted by NAI treatment, especially if instigated soon after illness onset. Of note, there was an increase in the mortality hazard rate with each days delay in initiation of treatment up to day five as compared with treatment initiated within two days of symptom onset.[3]

The causative virus, A(H1N1)pdm09, remains in circulation worldwide as a seasonal influenza virus, and continues to cause severe illness and death. While observational studies have limitations and weaknesses compared to RCTs, they may nevertheless help inform clinical practice, especially when no data from suitably powered placebo-controlled RCTs of NAI treatment in hospitalised influenza patients are available or planned. Given seasonal attack rates of <5% for symptomatic influenza confirmed by polymerase chain reaction (PCR),[11] and similar influenza virus detection rate in patients with community-acquired pneumonia,[12] RCTs that test NAIs for severe morbidity and mortality outcomes will be exceedingly challenging. Hence the consistency with which clinically meaningful benefits from observational studies of NAI treatment have been reported make such a body of evidence difficult for

clinicians, policy makers, and ethical committees to ignore. Accordingly, we advocate early NAI treatment for those prone to severe disease and in those hospitalized with influenza, in line with national public health guidance.

Regarding stockpiling of NAIs for pandemic deployment, the pandemic threat from emergent influenza A viruses such as A(H7N9) and A(H5N1) persists. Although these lack current person-to-person transmissibility, pandemic planners must consider all evidence and weigh this against the risks of inaction and the likely public outcry if potentially life-saving drugs are not available in the face of unpredictable, but potentially severe, future influenza outbreaks.

To conclude, the findings of the Cochrane Collaboration and those from observational studies are not in conflict. They provide evidence on different outcomes, for different groups of patients and across different settings. What matters is being able to reduce risk, mitigate the complications of influenza and save lives. Neuraminidase inhibitors remain an essential part of our armamentarium to lessen the impact of influenza.

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All authors drafted the manuscript

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Declarations of interest

Between October 2007 and September 2010, Jonathan S Nguyen-Van-Tam (JSN-V-T) undertook *ad hoc* paid consultancy and lecturing for several influenza vaccine manufacturers (Sanofi-Pasteur MSD, Sanofi-Pasteur, GlaxoSmithKline plc (GSK), Baxter AG, Solvay, Novartis) and manufacturers of neuraminidase inhibitors (F. Hoffmann-La Roche: oseltamivir (Tamiflu®) and GSK: zanamivir (Relenza®)). He is a former employee of both SmithKline Beecham plc (now part of GSK), Roche

Products Ltd. (UK), and Sanofi-Pasteur MSD, all prior to 2005. He has no outstanding interests related to shares, share options or accrued pension rights in any of these companies. He is in receipt of current or recent research funding, related to influenza vaccination from GSK and Astra-Zeneca and non-financial support (travel) from Baxter AG. His brother became an employee of GSK in January 2014. 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 et al, cited in the article. Karl G Nicholson (KGN) undertook *ad hoc* paid consultancy and educational presentations relating to the evaluation of neuraminidase inhibitors (F. Hoffmann-La Roche: oseltamivir (Tamiflu®) and GSK: zanamivir (Relenza®)) and received grant support for RCTs of both drugs (cited in the Cochrane review) more than 10 years ago. He was a founding member of the European Scientific Working on Group on Influenza (ESWI) and resigned in 2001. During 2006-07, he participated in an investigator-led study of neuraminidase inhibitor resistance with grant support from F. Hoffmann-La Roche. Within the last 5 years he received H5 vaccines from Novartis for MRC-funded research and H1N1 pandemic vaccines from GSK and Baxter for NIHR-funded research. Before 2010, he undertook *ad hoc* paid consultancy and delivered educational presentations for various influenza vaccine manufacturers (Baxter, Berna Biotech, Esteve, Novartis and GSK. Travel and accommodation expenses were reimbursed for attendance at the above *ad hoc* consultancy meetings, educational presentations, ESWI Board meetings, and an ESWI conference in 2008. Peter Openshaw (PJO) is vice-president of the European Scientific Working-group on Influenza (ESWI) and has served as a scientific advisor to GlaxoSmithKline, Sanofi and Janssen.

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