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REVIEW

Neuraminidase inhibitors: who, when, where?

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Abstract

Although the neuraminidase inhibitors (NIs), oseltamivir and zanamivir were first licensed in 1999, their clinical effectiveness is still hotly debated. Two rigorous systematic reviews and meta-analyses of the data from clinical trials conducted in community settings against relatively benign influenza, both suggest that reductions in symptom duration are extremely modest, under one day. Whilst one of these reviews could find no evidence of reductions in complications, the most recent review reported clinically meaningful and statistically significant reductions in the likelihood of requiring antibiotics (44%) and hospitalizations (63%) in adult patients with confirmed influenza, treated with oseltamivir. A further meta-analysis of observational data from the 2009 influenza A(H1N1) pandemic suggested that, in hospitalised patients, NIs significantly reduced mortality in adults by 25% overall, and by 62% if started within 48 hours of symptom onset, compared with no treatment. But, the effectiveness of NIs in children is far less clear. Taken together, these data suggest that NIs should be reserved for patients with influenza who are at high-risk of complications, or when clinically assessed found to be markedly unwell, or rapidly deteriorating. In such patients, treatment should be initiated empirically, as soon as possible, preferably with follow-on virological confirmation.

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Up until 1999, influenza management involved vaccination for primary prevention, and use of M2-inhibitors (amantadine and rimantadine) for prophylaxis and treatment. The latter were problematic medicines to use, owing to rapid emergence of resistance (especially when used for treatment and prophylaxis in the same setting and in immunocompromised patients) [1,2], absence of activity against influenza B, and frequent central nervous system side-effects (most often observed with amantadine; e.g. anxiety, hallucinations, nightmares and confusion), particularly in elderly subjects in whom the elimination half-life may be doubled [3].

From 1999 onwards, the neuraminidase inhibitors (NIs), zanamivir and oseltamivir, have offered new prospects for influenza management, being active against influenza A and B and with, overall, a more benign side-effect profile (albeit with a very common reported incidence of headache and nausea for oseltamivir) [4]. Notwithstanding, up until the A(H1N1)pdm09 pandemic in 2009, adoption and usage of NIs had been low in all territories except Japan. The 'Achilles Heel' of the NIs has always been their rather modest effect on symptom reduction [4], and somewhat limited historical evidence of their ability to reduce complications [5]. The combination of needing rapid access to treatment after symptom onset, and poor discriminatory powers of physicians to distinguish influenza clinically from a variety of other common respiratory virus infections, add further logistic and clinical challenges [6–8]. Taken together, the latter two elements could encourage inappropriate use of primary-care services for non-serious, self-limiting respiratory virus infections, produce logistic hurdles in terms of rapid access to treatment, and result in NIs being used to 'treat' a variety of non-influenza-related respiratory virus infections. The response of guidance authorities to this clinical conundrum has, in general,

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been to attempt to rationalize limited use of NIs in situations where diagnostic certainty of influenza is enhanced, access to treatment is timely, and the patient is less likely to have uncomplicated influenza infection [9]—essentially periods when influenza is known to be circulating widely, and use in high-risk patients who can be treated rapidly after symptom onset.

The above scenario was in sharp contrast to policy evolution over use of NIs in the event of a pandemic. In this arena, in 2005, responding to the pandemic threat posed by avian influenza A(H5N1) in particular, the WHO recommended the establishment of a global stockpile of antiviral drugs [10]; and recommended that countries with sufficient resources should also acquire individual national stockpiles [10]. These stockpiles were subsequently deployed widely during the 2009 pandemic, albeit not against A(H5N1) but the much less virulent A(H1N1) pdm09 virus. In the aftermath of this event, further questions have been raised about the rationale of stockpiling NIs for pandemic usage, and their clinical effectiveness. Recent debate has been polarized by an updated Cochrane review [11], which has been used to suggest that NIs are hardly effective, and should not be used or stockpiled; and a global individual participant data (IPD) meta-analysis (the PRIDE study) suggesting that NIs reduced mortality during the pandemic [12]. Where do such apparently disparate conclusions leave the frontline microbiologist or infectious diseases physician in terms of the management of patients, and the giving of advice to others?

In the *Summary of Product Characteristics*, oseltamivir is stated to reduce the duration of influenza symptoms by 1 day in adults and 1.5 days in children [4], with similar figures for zanamivir [13]. In the latest systematic review and meta-analysis of clinical trials data performed by the Cochrane collaboration, these modest effects were confirmed; oseltamivir reduced time to alleviation of symptoms of influenza-like illness in adults by 16.8 h and by 29 h in children [11]. The authors of the Cochrane review could find no significant effects on pneumonia, serious complications, hospitalizations or deaths, leading them to state that 'treatment trials do not settle the question whether the complications of influenza (such as pneumonia) are reduced, because of a lack of definitions' [11]. Although the Cochrane review identified 107 reports (some unpublished and not previously made available) only 46 were included in the meta-analysis. At least as importantly the clinical trials examined were all conducted in the setting of 'relatively benign influenza' [11] in the community, which occurred during normal winter seasonal periods. Under such circumstances it is difficult to determine if the absence of any statistically significant effect on complications amounts to evidence of no effect; or if in fact sampling bias would have been the real issue because of failure to use all of the available data, and a low frequency of complications (and only two influenza-related deaths) in a study sample comprising relatively mild influenza cases.

An alternative analysis of the clinical trials data for oseltamivir treatment in adults has subsequently been published, initiated by the Multi-party Group for Advice on Science (MUGAS) Consortium [14]. Conducted independently of the manufacturer, this new analysis considered all of the clinical trials data for oseltamivir and adopted an IPD approach. Like systematic reviews, an IPD analysis aims to summarize the evidence from multiple studies investigating the same research question. However, unlike a systematic review, which relies on published estimates of treatment effect from various studies that may not be directly comparable because of varying clinical case definitions and treatment regimens, an IPD approach collates individual patient-level data from the source studies, and applies standard definitions and techniques to arrive at a single pooled effect estimate [15]. Using such an IPD approach, Dobson and colleagues showed that the reduction in time to alleviation of influenza symptoms in adults was remarkably similar to that described in the Cochrane review (which did not use an IPD approach); but in sharp contrast, reductions in lower respiratory tract complications requiring antibiotics associated with oseltamivir treatment were clinically important and highly significant in both the intention-to-treat population (38% reduction; $p < 0.0001$) and the intention-to-treat influenza-confirmed population (44% reduction; $p < 0.0001$). More importantly, hospitalizations were also significantly reduced in the intention-to-treat influenza-confirmed population (63% reduction; $p = 0.013$) but not in the intention-to-treat population (39% reduction; $p = 0.066$). By using a superior methodological technique, these new data offer a robust challenge to the previous interpretation of the clinical trials data on oseltamivir in relation to the reduction in complications of public health importance, since in most major healthcare systems emergency hospitalization is a potent cost driver and there is an imperative to reduce antibiotic usage. These new data underscore the importance of treating high-risk patients (those at elevated risk of hospitalization) with NIs if they present early with symptoms of seasonal influenza.

Data derived from community settings and in the context of relatively mild seasonal influenza are not easily generalizable to hospitalized patients with severe influenza; or a pandemic scenario in which a novel virus, combined with high levels of population susceptibility, produce widespread morbidity and mortality. Evidence to inform clinical decision-making in these settings should ideally be derived from those settings; but in both cases, randomized trials are unlikely to prove ethically feasible, placing greater reliance on observational data. Observational studies are generally considered methodologically inferior to experimental study designs that involve random

allocation of treatment to patients. Randomization of treatment allocation ensures that treated and non-treated groups differ only by chance, whether in terms of pre-existing comorbidities, illness severity or other (measured or unmeasured) clinical characteristics; typically this produces balanced arms that, in turn, give greater confidence that any observed differences in outcomes can be attributed to treatment effects. On the other hand, observational studies investigating treatment effects are prone to 'confounding by indication' because real-life treatment decisions are influenced by a patient's clinical characteristics and the attending physician's behaviour; this means that there is less certainty about attributing an observed outcome to treatment effects. This is why a systematic review of published observational studies investigating the association between NI antiviral use during the 2009 influenza pandemic and patient outcomes only cautiously concluded that a statistically significant 65% mortality reduction in early treated versus untreated patients suggested a meaningful public health benefit [16]. Recent developments in methodological approaches, such as propensity scoring, make it possible to use observational data for evaluating treatment effects with greater confidence; however, they can only be used when detailed individual level data on patient characteristics are available. Propensity scores are a statistical method of addressing confounding by indication when investigating treatment effects; essentially, they predict the likelihood of treatment based on a specified set of patient characteristics [17]. Once propensity scores have been calculated, researchers can adjust for varying treatment propensity or match study subjects on propensity scores to create more equivalent groups that approximate to randomly allocated treatment groups in a randomized controlled trial. A limitation of propensity scoring methods is that they can only account for known confounders and if important covariates are omitted from the propensity score derivation model, this will introduce a bias in the results.

The largest and most convincing study of observational data from the 2009–10 pandemic period, using an IPD approach and propensity scoring, provides further evidence that NIs reduced mortality in patients hospitalized with pandemic influenza [12]. The study included 29 234 hospitalized subjects worldwide, of whom 86% had laboratory-confirmed A(H1N1)pdm09 infection and showed that mortality in adults was reduced by 25% overall ($p = 0.0002$, treatment at any time versus none), and by 62% ($p < 0.0001$) if treatment was started within 48 h of illness onset [12]. But the findings were not statistically significant in children. Of further note, late treatment ($\geq$48 h of symptom onset) of adults requiring intensive care still resulted in a mortality reduction of 35% ($p = 0.0183$) [12]. Although the authors were careful to adjust for treatment propensity, they acknowledged that residual confounding by indication was possible given the source data limitations. They were also unable to adjust completely for disease severity because of the heterogeneity of severity measures across individual source studies. Time-dependent treatment effects can also impact the analysis of observational data, such that treatment can appear to be favourable compared with no treatment because of 'immortal time bias' [18,19]—essentially, patients who die early do not get an opportunity to receive treatment. In the PRIDE study [12], the researchers used well-accepted techniques to account for this potential bias by only considering survival time after treatment was initiated in the treated group [19]. Such analyses still cannot account fully for other time-dependent biases that may be at play, such as delayed admission following illness onset; but, as of now, there is no consensus among statisticians about the best approach to deal with all these biases, simultaneously, in a single statistical model. Notwithstanding, the PRIDE investigators subsequently presented an array of results obtained from a number of alternative statistical models, and all seem to support the conclusion that NIs were associated with a significant reduction in mortality [20]. Therefore, in the absence of a randomized controlled trial, this IPD analysis of observational data remains, to date, the most methodologically robust evidence on NI effectiveness in the context of patients hospitalized with influenza.

What then should microbiologists, infectious disease physicians and pulmonologists advise in day-to-day practice? Taken together, what advice can be summarized from the Cochrane review [11], the analysis by Dobson and colleagues [14], and the PRIDE study [12]? Most cases of influenza will be mild, and managed in primary care without the use of viral diagnostic tests or the involvement of secondary-care physicians. Here, given the modest effect of NIs on reduction in symptom duration observed consistently across two meta-analyses [11,14], early treatment of influenza-like illness should be emphasized for high-risk patients at elevated risk of hospitalization, and other patients who are markedly unwell or obviously deteriorating; in both cases, NIs may well exert a protective effect and avert hospitalizations or complications.

In hospitals, where patients admitted with influenza, by definition, have severe infection and may already be several days into the illness (after symptom onset), NI treatment should be presumptive, based on clinical suspicion of influenza; and immediate, with the emphasis on instigating therapy as early as possible, without waiting for virological confirmation. This might occur alongside antibiotic treatment if a bacterial aetiology cannot be firmly excluded, because bacterial pneumonia is a frequent complication in patients who are hospitalized with influenza [21]. If adequately taken respiratory specimens later fail to confirm influenza (or reveal an alternative virus aetiology) NIs can be stopped at that juncture.

In terms of strengthening the evidence for the future, and assuming, somewhat realistically, that randomized trials will not be possible in patients with severe influenza, new studies need

to focus on collecting adequate, standardized data on illness onset and progression, comorbidities, disease severity, treatment (particularly NIs, corticosteroids and antibiotics, along with detailed treatment regimens), outcomes such as influenza-related pneumonia (with radiological and microbiological results), need for and duration of critical care, length of stay in hospital, and influenza-related mortality; to facilitate more sophisticated survival analyses, exact dates of illness onset, admission to various levels of care, start of treatment, diagnostic tests, outcomes and length of follow up are also required.

Transparency declaration

JSN-V-T was employed by SmithKline Beecham (now a part of GlaxoSmithKline—manufacturer of zanamivir) from 2000 to 2001 and by Roche Products Ltd (manufacturer of oseltamivir) from 2001 to 2002. He has held no shares, share options or pension rights in either company since 2004. He performed paid consultancy for both companies in the period 2008 to 2010. He received a travel bursary from the European Scientific Working Group on Influenza (ESWI) to deliver a plenary lecture unrelated to neuraminidase inhibitors, at an open scientific meeting. He is currently in receipt of research funding from GlaxoSmithKline (for vaccines work, and a PhD studentship). He has current funding from F. Hoffmann-La Roche which has supported two studies cited in this article [12,16,20]; SV, SGM and PRM have been involved in these studies. PRM has received a travel bursary from Genentech for a lecture on methodological approaches to studying treatment outcomes in influenza patients. SV and SGM report no conflicts of interest.

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