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Corresponding Author:	Tristan Clark, MD University of Southampton Southampton , Hampshire UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Southampton
Corresponding Author's Secondary Institution:	
First Author:	Tristan Clark, MD
First Author Secondary Information:	
Order of Authors:	Tristan Clark, MD
	Kate R Beard
	Nathan J Brendish
Order of Authors Secondary Information:	

Treatment of influenza with neuraminidase inhibitors

Kate R Beard[a] Nathan J Brendish[a,b], and Tristan W Clark[a,b,c,d,*]

a Academic Unit of Clinical and Experimental Sciences, University of Southampton, Southampton, UK.

b Department of Infection, University Hospital Southampton NHS Foundation Trust, Southampton, UK.

c NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK.

d NIHR Post-Doctoral Fellowship Programme.

*Corresponding author

Dr Tristan William Clark, Associate Professor and Honorary Consultant in Infectious Diseases

Address: LF101, South Academic block, Southampton General Hospital, Southampton, SO16 6YD.

Tel: 0044(0)2381208410 E-mail address: T.W.Clark@soton.ac.uk

Abstract

Purpose of review: Seasonal and pandemic influenza are major causes of morbidity and mortality globally. Neuraminidase inhibitors (NAIs) are the only class of antiviral agent recommended for the treatment of currently circulating strains of influenza. There has previously been controversy over the level of evidence for patient benefit with NAIs. We review here the current evidence base for the clinical impact of treatment of influenza with NAIs.

Recent findings: Meta-analysis of pharma sponsored studies (including previously unpublished data) shows that NAIs reduce the duration of illness in influenza infected patients, and suggest a possible reduction in the rate of complications and hospitalisation. Meta-analysis of observational studies examining oseltamivir use during the H1N1 2009 pandemic, suggest a reduction in hospitalisation rate in community dwelling patients and a reduction in mortality in hospitalised adults treated with NAIs. Current NAI use in the community and hospitals varies widely but in general they are underutilised.

Summary: Although there has been controversy over the level of evidence for patient benefit, a growing body of evidence suggests that treatment of influenza with NAIs is associated with improved outcomes for both patients in the community and more severely unwell patients in hospital. Clinical outcomes are optimal with earlier use and strategies to improve early widespread NAI utilisation are needed.

Keywords

Neuraminidase inhibitors, influenza, oseltamivir, zanamivir

Introduction

Neuraminidase inhibitors (NAIs) represent the only drug class currently recommended for the treatment of influenza [1-3]. During the 2009 influenza pandemic NAIs were implemented as the key pharmacological intervention in addition to vaccination, and had been stockpiled by many public health agencies in preparation for such an event [4-6]. Despite the global experience of using NAIs during the pandemic some evidence gaps remain to be addressed to inform planning for future pandemic events and appropriate deployment in seasonal influenza infection.

NAIs are highly selective competitive inhibitors of neuraminidase, a glycoprotein located on the influenza virus membrane. Neuraminidase promotes the liberation of progeny virions from the infected host cells, by cleaving sialic residues on cell-surface receptors which are key attachment sites for influenza A and B viruses, therefore making it a key drug target within the viral replication cycle. Inhibition of this process is the accepted mechanism by which NAIs exert their influenza-specific anti-viral effect [7-9].

Establishing the crystal structure of the highly conserved antigen neuraminidase in 1983 [10], allowed rational computer-assisted drug design, and the development of the highly selective reversible neuraminidase inhibitor, zanamivir (GSK, London, UK), first approved for use in 1999. An inhibitor of influenza A and B neuraminidases and delivered by the inhalation route, zanamivir had clear advantages over the M2 inhibitors amantadine and rimantadine, whose anti-viral spectrum is restricted to Influenza A and has been subsequently complicated by widespread resistance in currently circulating strains. The oral NAI oseltamivir (F.Hoffman-La Roche, Basel, Switzerland) was subsequently developed following modifications including the use of a cyclohexene ring and lipophilic side chain [7-9, 11], and is globally now the most commonly used NAI. During the first eight months alone of the H1N1 2009 influenza pandemic it is estimated that more than 18 million people worldwide received oseltamivir [12].

The most recent additions to the NAI class are peramivir, delivered as a single intravenous dose and laninamivir delivered as a single inhalational dose, both active against influenza A and B. Their use to date has been limited however, with laninamivir currently only approved for use in Japan and peramivir approved for use in USA, Japan, South Korea and China [8]. Intravenous zanamivir has since been used on a compassionate basis for severely ill patients with a poor clinically response to oseltamivir and suspected or proven resistance [1]. It has been evaluated in a phase 2 randomised controlled trial and was shown not to be superior to standard doses of oral oseltamivir in adults with oseltamivir-sensitive influenza [13]. Table 1 shows the different NAIs and their properties.

Approaches to NAI treatment strategies within the 2009 pandemic worldwide ranged from no use, the targeted use for high risk individuals (most common) and a 'treat all' strategy for patients presenting with clinical illness, which was consistently applied within Japan [6]. These strategies employed NAIs (most commonly oseltamivir) as monotherapy. Trials evaluating the impact of combinations of antivirals (including adamantanes and ribavirin) have had conflicting results. A recent phase 2 double-blinded RCT did not find a combination of oseltamivir, amantadine and ribavirin to be associated with improved clinical outcomes compared to oseltamivir monotherapy [14].

National and international guidelines

UK Public Health England (PHE) guidelines [1] recommend the use of NAIs in the following situations:
Suspected or confirmed,

- Uncomplicated influenza in patients with risk factors for the development of complicated infection, within 48 hour of symptom onset or later at clinical discretion
- Complicated influenza, including after 48 hours of symptom duration

Treatment is recommended to start as early as possible and without waiting for laboratory confirmation due the delays in obtaining results from centralised laboratory testing. Definitions of uncomplicated and complicated influenza are given in table 2. Risk factors for development of complications are shown in table 3. PHE guidelines are strongly aligned with US CDC [3] and WHO guidelines [2].

Evidence in patients with uncomplicated influenza in the community

In 2014 a Cochrane review evaluated randomised controlled trial data on neuraminidase inhibitor use including previously unavailable pharmaceutical company study reports and regulators' comments. The Cochrane group examined data from 46 trials (20 oseltamivir and 26 zanamivir studies) for both treatment and prophylaxis in adults and children. The conclusions of the Cochrane review were that both drugs decreased the duration of influenza-like illness symptoms by around 0.5 to 1 day in adults. Considerable heterogeneity complicated the results for children. They reported that the effect of NAI treatment on the development of pneumonia and other complications was unreliably recorded in the trials for oseltamivir, preventing any firm conclusions. Oseltamivir use was associated with an increased risk of nausea, vomiting, renal and neuropsychiatric disorders [15, 16].

The major weakness of the Cochrane review is that the studies analysed in it mainly involved community-dwelling healthy participants and excluded patients with significant comorbidities. Mortality was therefore a rare event, and the trials were not methodologically designed or powered to reliably detect differences in complications including hospitalisation [15, 17]. The Cochrane review analyses therefore does not evaluate the patient groups who are most likely to benefit from influenza treatment, i.e. those with comorbidities that put them at high risk of complications and those hospitalised with already severe influenza-related illness.

A subsequent meta-analysis (funded by an unrestricted grant from Roche) used individual patient data from nine randomised placebo controlled trials of oseltamivir involving 4328 adult patients with influenza infection and demonstrated a similar reduction in the duration of symptoms to that seen in the Cochrane review. In addition they concluded that oseltamivir treatment of influenza reduced the risk of lower respiratory tract complications and hospitalisation. Although this analysis was based on the same trials included in the Cochrane review, the authors argue that using individual patient data rather than summative study reports allows a more thorough analysis of outcomes. This study also demonstrated an increased risk of nausea and vomiting with oseltamivir but did not find an association with neuropsychiatric disorders [18].

A large randomised placebo controlled trial of NAI treatment in uncomplicated influenza in Bangladeshi children showed a reduction in symptom duration of around 1 day and reduced viral shedding even when treatment was commenced 48 hours or longer after symptom onset, although the benefit was greatest in those treated within 48 hours. This study did not evaluate the effect of NAIs on complications or hospitalisation [19].

A meta-analysis of observational studies from the H1N1 2009 pandemic and using individual participant data from 3376 patients, evaluated the effect of NAI treatment on hospital admission in patients with influenza (91% of which was laboratory confirmed) in the community and outpatient settings. It suggested that treatment with NAIs was associated with a reduced likelihood of hospital admission and that earlier treatment (<48 hours of symptoms duration) was more beneficial than later treatment [20]. Another meta-analysis of four observational studies including pre and post pandemic studies also suggested a reduction in hospitalisation rate with oseltamivir treatment of outpatients but these studies did not adjust for important patient factors and were therefore deemed to be at high risk of bias [21].

Evidence in hospitalised patients with complicated influenza

In contrast to the evidence base for NAI efficacy in the community setting, data in hospitalised patients is limited to observational studies, the interpretation of which is complicated by the inherently higher risk of bias in this type of study. Prior to the H1N1 2009 pandemic, several small observational studies evaluated the impact of NAI treatment in seasonal influenza, often in specific patient groups [22-26].

Pre-pandemic

Most pre-pandemic studies suggested that NAI treatment was associated with a reduction in mortality. A systematic review and meta-analysis of data including studies of hospitalised patients with seasonal influenza concluded that oseltamivir may be associated with reduced mortality compared to no antiviral treatment in high risk populations. The overall quality of the evidence however was low due to the risk of confounding, selection and publication bias [21].

Post pandemic

A systematic review and meta-analysis of patients of any age hospitalised in the H1N1 2009 H1N1 pandemic did not find a significant reduction in mortality with NAIs given at any time vs no treatment. However, a reduction in mortality was found with early (<48 hours after symptom onset) vs late treatment (>48 hours after symptom onset), and with early treatment vs no treatment [27]. This was similar to the time-specific benefits seen in earlier observational studies [21]. Limitations of this analysis included heterogeneity of included studies and potential incomplete adjustment for confounding variables [27]. The authors postulate that the reason for the lack of an observed mortality benefit with NAI treatment vs none was due to confounding by indication, so that more severely unwell patients were more likely to receive NAI treatment. They also noted a high degree of heterogeneity among included studies and a likely publication bias.

The same authors performed a subsequent meta-analysis using individual participant data from nearly 30,000 patients (including adults and children) hospitalised with pandemic H1N1 2009

influenza [6]. Propensity scoring was used to adjust for confounding variables. In this analysis, a significant reduction in mortality was observed with NAI treatment at any time vs no NAI treatment. The mortality benefit of NAI treatment was not seen with commencement after 48 hours of symptoms duration in the main cohort but was maintained beyond 48 hours of symptoms duration in patients admitted to critical care units, suggesting continued benefits even with late administration in more severely unwell patients. Amongst children (aged <16 years) the association between NAI use and mortality benefit did not reach statistical significance, however NAI treatment at any time versus none was found to significantly reduce mortality in pregnant women, a patient group identified as high risk by Public Health England [1, 4].

Current use of NAIs in clinical practice

Internationally there is a great variation in the use of NAIs [5, 28, 29]. Despite the potentials benefits of NAI treatment, studies suggests that most community dwelling patients with influenza who are at high risk of complications do not seek medical attention early enough during their course of illness for optimum NAI treatment. Even when patients do present early only a minority are tested and prescribed an antiviral medication in line with guidelines recommendations [30-32]. For hospitalised patients, treatment of suspected seasonal influenza with NAIs appears to have increased following the H1N1 2009 pandemic [33, 34] but still remains suboptimal and is often delayed due to the slow turnaround time of laboratory testing [35].

Most national guidelines recommend the empirical use of NAIs in patient with suspected influenza prior to the results of laboratory testing due to the slow turnaround time for test results and the need for prompt treatment [1-3, 5]. As the accuracy of clinician diagnosed influenza is low [36, 37] this strategy exposes a large number of patients who do not have influenza to NAIs with the consequential risk of side effects such as nausea and vomiting [1-3, 38]. Although they are used in many counties, antigen-based rapid diagnostic test (RDTs) and digital immunoassays (DIAs) for

influenza lack sensitivity [39-41] and have not been shown to be of clinical benefit or cost effective in a randomised controlled trial [42]. Newer rapid molecular test platforms have equivalent diagnostic accuracy to laboratory PCR and can be used at the point-of-care to direct NAI use [43-45]. Recently a large randomised controlled trial demonstrated that routine molecular point-of-care testing for respiratory viruses in hospitalised adults was effective in increasing the early detection of influenza and preventing unnecessary NAI exposure in influenza-uninfected patients, in addition to other benefits including the rational use of isolation facilities [46, 47].

Conclusion

There is a growing body of evidence that neuraminidase inhibitor use (mostly oseltamivir) for the treatment of influenza is associated with improved clinical outcomes. In community dwelling patients randomised controlled trials have shown a reduction in the duration of illness but have not reliably shown a reduction in the rate of complications or hospitalisation. Subsequently observational studies from the H1N1 2009 pandemic have suggested a reduction in the rate of hospitalisation in patients in the community. For hospitalised patients, there have been no placebo controlled randomised controlled trials evaluating the impact of NAI treatment but observational studies including a very large and well controlled meta-analysis from the H1N1 2009 pandemic suggests a reduction in mortality with NAI use in adults. Evidence in all groups consistently demonstrates that earlier administration is associated with the greatest benefit. Current utilisation of NAIs for influenza, especially in the community is sub-optimal. Although some have argued for definitive randomised placebo controlled trials of NAIs in hospitalised patients [48], such trials are ethical difficult to justify given the widespread use of NAIs in standard care for influenza in hospitals. Strategies that improve the detection of influenza and the early use of NAIs are needed and may include the routine use of molecular point-of-care testing.

Key points

- Randomised placebo controlled trials demonstrate that NAIs reduce the duration of influenza symptoms in community dwelling patients but increase the risk of nausea and vomiting.
- Observational data suggests a reduction in hospitalisation with outpatient NAI treatment in community dwelling patients
- Well controlled observational data suggests that NAI use reduces mortality in hospitalised adults with influenza especially when given early in the course of illness. This is aligned with national and international guidelines in recommending the liberal early use of NAIs in hospitalised patients

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Conflicts of interest

TWC has performed paid consultancy work for Janssen, Roche diagnostics, Synairgen Research Limited and Planet Innovation. He has received speaker fees and travel fees from BioFire Diagnostics, LLC and BioMeriuex. He has received discounted equipment and consumables for the purposes of research from BioFire Diagnostics, LLC. He has acted as chief or principal investigator in clinical trials of antivirals sponsored by Gilead Sciences and Janssen. He has enrolled patients into clinical trials sponsored by Novartis, GlaxoSmithKline and Baxter Pharmaceuticals. NJB has recruited patients into clinical trials sponsored by Janssen and Gilead Sciences. TWC is the holder of an NIHR Post-Doctoral Fellowship. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute of Health Research, or the Department of Health.

Table 1. Neuraminidase inhibitor agents and their properties

Agent	Route of administration	Dose and interval	Duration of course	Common and notable side effects	Comments
Zanamivir	Inhaled	10mg bd	5 days	Bronchospasm	Approved worldwide
	Intravenous	600mg bd	5-10 days*		
Oseltamivir	Oral	75mg bd	5 days	Nausea and vomiting	Approved worldwide
Peramivir	Intravenous	600mg od	Single dose or 5-10 days *	Diarrhoea	Approved in US, Japan, South Korea and China only.
Laninamivir	Inhaled	40mg	Single dose	Unknown	Approved in Japan only

**Severe influenza in hospitalised patients, unlabelled use.

Table 2. Definitions of complicated and uncompleted influenza

Uncomplicated influenza	Complicated influenza
Influenza presenting with fever, coryza, generalised symptoms (headache, malaise, myalgia, arthralgia) and sometimes gastrointestinal symptoms, but without any features of complicated influenza.	Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, lung infiltrate), central nervous system involvement and/or a significant exacerbation of an underlying medical condition

Table 3. Risk factors for complicated influenza

Risk Factor
Neurological disease
Hepatic disease
Renal disease
Pulmonary disease
Cardiac disease
Diabetes mellitus
Severe immunosuppression
Age over 65 years
Pregnancy (including up to two weeks post-partum)
Children under 6 months of age
Morbid obesity (BMI ≥40)

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