Oseltamivir for prevention of influenza and related morbidity in at-risk patients during outbreaks in care homes and similar settings: evidence summary and review of risk-benefits

Conall Watson MPharm DipGPP PhD FFPH, consultant in health protection, seasonal flu lead, Public Health England South East Centre. PHE Chilton (Thames Valley Team) conall.watson@phe.gov.uk

1 Sep 2020, v2.0

Key points

This evidence summary focuses on the evidence base for oseltamivir antiviral as chemoprophylaxis in prevention of influenza during ongoing outbreaks in care homes and similar settings, as well as its treatment role in such settings. Antivirals are recognised have modest efficacy in relief of symptomatic flu in the general population, reducing symptoms by about a day in otherwise healthy adults – this is distinct from prophylactic and treatment use in care homes, or treatment of frail older adults, where the case for use is stronger.

Public Health England (PHE) [1-3] **and NICE** (TA168 & CKS 2015) **recommend using antivirals for influenza outbreaks in residential care settings.** A much-debated 2014 Cochrane review [4] recommended against widespread use of oseltamivir in the general population for flu treatment and prophylaxis. Setting aside views on the validity of the review's conclusions, these are different indications to treating frail poly-comorbid ("at-risk") patients at higher risk of severe complications, or using antivirals to prevent illness in outbreaks in at-risk populations, such as care home residents.

There is evidence from trials that oseltamivir has high efficacy in preventing symptomatic flu when used as prophylaxis [5, 6]. The Cochrane analysis put this at 55% efficacy in the general population and **80% in post-exposure settings** [4]. This protective effect includes vaccinated frail care home residents [7]. Analysis of household pairs found that **treating cases reduces illness in their contacts by about 80%**, on top of the preventative effects from prescribing oseltamivir to the contacts [8, 9]. Furthermore, averting flu infection in contacts means they do not transmit to others, creating additional indirect protection that is not accounted for in individually-randomised controlled trials.

Oseltamivir is likely to reduce the risk of serious outcomes in treated flu patients. Individual patient meta-analysis of the oseltamivir treatment trials suggests approximately 60% reduction in risk of all-cause hospital admissions (0.6% vs 1.7%) [10]. Individual-patient meta-analysis of oseltamivir use in the H1N1 pandemic suggests approximately 20% reduction in mortality in flu-hospitalised patients, with approximately 50% reduction in mortality when initiated within 48hours of symptom onset [11]. A recent international randomised controlled trial led by University of Oxford primary care found that older, sicker, comorbid patients with longer prior symptoms recovered 2 to 3 days sooner with oseltamivir than untreated patients.[12]

In terms of side effects from oseltamivir chemoprophylaxis, the safety profile remains favourable [13]. Nausea in the first two days is very commonly reported (>10%) and transient. Headache is also a very common side effect. Abdominal pain, vomiting, insomnia and dizziness are amongst common side effects. While clinicians should be vigilant for severe adverse events, these are not common in post-marketing surveillance.

The current NICE technology appraisal (TA168), which accounts for benefit and risks, indicates that **oseltamivir is highly cost-effective when used in prophylaxis of at-risk patients, relative to other NHS activity (not just against the NICE threshold)**. Cost-effectiveness would be higher still if accounting for the specific scenario of a care home outbreak, including the health gain from indirect protection which was not included in the NICE appraisal.

Where there is uncertainty in renal function of care home residents, pragmatic dose reduction can be used (British Geriatrics Society in [3]).

Approved by APCO Sept 2020

Background

Influenza antivirals in the neuraminidase inhibitor class such as oseltamivir (Tamiflu®, Roche) and zanamivir (Relenza®, GSK) can have an important role in treating patients, preventing infection and interrupting transmission of flu outbreaks in closed setting such as residential care homes. This can reduce morbidity, hospital admissions and mortality in vulnerable patients.

PHE health protection teams commonly recommend prescribing oseltamivir for this indication in line with NICE guidance, however, the evidence base and risk-benefit are not widely appreciated or clearly articulated. In particular, confidence in antivirals has been dented by a 2014 Cochrane neuraminidase inhibitor review [4], widely covered in the BMJ, which used previously unpublished regulatory data as part of the systematic review. This review has a number of methodological and reporting issues, some of which are detailed in published feedback (p515-549), with the authors noting their analysis of the side effects requires further details such as age stratification (p526). It is important to note that the focus of the Cochrane review is on the stockpiling and widespread use of antivirals in the general population, particularly in treatment, such as for pandemic or seasonal prophylaxis (p5), and that it specifically excludes observational data, limiting ability to make inference about less common outcomes.

Oseltamivir prophylaxis efficacy

The 2014 Cochrane review prophylaxis findings are consistent with other reviews [9, 14] in recognising that there is high efficacy in chemoprophylactic use of oseltamivir to prevent symptomatic flu [4], reporting separately as 55% efficacy in individual seasonal prophylaxis (RR 0.45, 95% CI 0.30 to 0.67) and 80% efficacy in post-exposure household use (RR 0.2, 95%CI 0.09 to 0.44). Asymptomatic lab-confirmed flu case numbers do not change significantly, but are fewer in number than symptomatic cases and have scant evidence to indicate infectiousness [15]. The overall effect is a reduction in the risk of developing laboratory-confirmed influenza, whether symptomatic or not. In a care home setting, reduction in second generation case numbers has the potential to reduce third and later generation case numbers through indirect protection.

Analysis of household studies by mathematical modellers has yielded further insights into the components of the transmission chain that can potentially be influenced by neuraminidase inhibitors [8, 9]. Table 1 below is a summary of effects from Yang et al [8], suggesting efficacy against disease and infection in contacts of confirmed flu cases, when giving oseltamivir to contacts. It also indicates that giving oseltamivir to cases reduces risk of symptomatic disease in their contacts, though it does not block infection. Other household studies have not found such an effect, though lack of power is reported [16].

The demonstrable efficacy of licenced neuraminindase inhibitors in prophylaxis is consistent with the reported mechanism of action. These drugs interfere with the release of progeny influenza virions from infected cells, preventing infection of new host cells [17]. Neuraminindase inhibitors may therefore be more effective in prevention of the development of new influenza illness than symptomatic relief of established disease.

Table 1. Efficacy of case-administered and contact-administered oseltamivir against influenza outcomes in household contacts of confirmed influenza cases.

		Person to whom oseltamivir is administered	
		Case	**Contact**
Efficacy (relative risk reduction) against outcome in the contact (95% credible interval)	**Infection (symptomatic or asymptomatic)**	-18% (-93% to 30%)	62% (39% to 77%)
	Symptomatic disease in contacts whom have been infected	84% (53% to 97%)	41% (-28% to 81%)
	Symptomatic disease (whether infected or not)	81% (42% to 96%)	77% (45% to 93%)

Adverse events in prophylaxis patients

A recent European Centre for Disease Control review of oseltamivir considers the safety profile of oseltamivir to be favourable for licensed indications [13], consistent with ongoing licensure by international drug regulatory authorities.

Single episodes of nausea on day one or two of treatment is very commonly reported (>10%) and considered to be transient [18]. Headache is also a very common side effect. Abdominal pain, vomiting, insomnia and dizziness are amongst common side effects. While clinicians should be vigilant for severe adverse events and discontinue where appropriate, these events are not common in post-marketing surveillance. [19]

Renal dosing in prophylaxis and dosing in older adults of uncertain renal function.

For care home outbreak response, it is not uncommon that treatment or chemoprophylaxis may be indicated for older adults with unknown renal function. In such situations, the British Geriatrics Society (BGS) advice is summarised as follows:

- If a renal function test in the last 6 months indicates no impairment, then standard doses should be used.
- Wide-scale renal function testing is logistically challenging in outbreak situations and likely to delay initiation of effective treatment/prophylaxis.
- For patients with known impaired renal function and information that the prescriber can access, dosage should be reduced in line with existing guidance [such as the SmPC [18] and/or the BNF].
- If there is no information (or none from the last 6 months) some renal impairment should be assumed and doses used for CrCl 31 to 60ml/min.
- Time permitting, higher risk patients such as those on potent diuretics could be prioritised for renal function checks.

Approved by APCO Sept 2020

Please see the full BGS advice in appendix 5 of the PHE guidance [3].

Should oseltamivir accumulate, it is generally adequately tolerated a higher doses. Increased doses have been examined for use in treatment of severe illness. Dose dependent side effects reported in a large pharmacokinetic study include higher incidence of nausea (around 31%) and vomiting (16%), headache frequency consistent with standard doses and no adverse effects on vital signs or cardiac function [20].

Treatment of at-risk patients for reduction in admissions and morbidity/mortality

Treatment in symptomatic at-risk patients is strongly supported by PHE [1, 2].

An individual-patient meta-analysis found in the region of 20% mortality reduction in hospitalised patients in the H1N1 pandemic (adjusted odds ratio [aOR] 0.81; 95% CI 0.70 to 0.93) [11]. This meta-analysis also supports prompt initiation of antiviral treatment, suggesting approximately 50% reduction in mortality if oseltamivir commences within 48h of symptom onset (aOR 0.50; 95% CI 0.37 to 0.67).

An individual patient meta-analysis of oseltamivir treatment trials found an approximately 60% relative reduction in all-cause hospital admissions (relative risk 0.37, 95% CI 0.17 to 0.81). The absolute risk reduction in treated patients was 1.1% (95% CI 0.3 to 1.4) from 1.7% baseline risk in placebo recipients [10].

A recent international randomised controlled trial led by University of Oxford primary care found that older, sicker, comorbid patients with longer prior symptoms recovered 2 to 3 days sooner with oseltamivir than untreated patients.[12]

References

1. Cosford, P., *The use of antivirals for the treatment and prophylaxis of influenza PHE summary of current guidance for healthcare professionals*. 2014: London, UK. p. 11-11.
2. group, P.H.E.a.w., *PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza, version 8.0*. 2017: London, UK. p. 39-39.
3. Public Health, E., *PHE guidelines on the management of outbreaks of influenza-like illness (ILI) in care homes*. 2017: London, UK.
4. Jefferson, T., et al., *Neuraminidase inhibitors for preventing and treating influenza in adults and children.* Cochrane Database of Systematic Reviews, 2014(4).
5. Welliver, R., et al., *Effectiveness of oseltamivir in preventing influenza in household contacts: A randomized controlled trial.* JAMA, 2001. **285**(6): p. 748-754.
6. Hayden, F.G., et al., *Management of Influenza in Households: A Prospective, Randomized Comparison of Oseltamivir Treatment With or Without Postexposure Prophylaxis.* The Journal of Infectious Diseases, 2004. **189**(3): p. 440-449.
7. Peters, P.H., et al., *Long-Term Use of Oseltamivir for the Prophylaxis of Influenza in a Vaccinated Frail Older Population.* Journal of the American Geriatrics Society, 2001. **49**(8): p. 1025-1031.
8. Yang, Y., M.E. Halloran, and Longini Ira M, Jr., *A Bayesian model for evaluating influenza antiviral efficacy in household studies with asymptomatic infections.* Biostatistics, 2009. **10**(2): p. 390-403.
9. Halloran, M.E., et al., *Antiviral Effects on Influenza Viral Transmission and Pathogenicity: Observations from Household-based Trials.* American Journal of Epidemiology, 2007. **165**(2): p. 212-221.
10. Dobson, J., et al., *Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials.* The Lancet, 2015. **385**(9979): p. 1729-1737.
11. Muthuri, S.G., et al., *Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data.* The Lancet Respiratory Medicine, 2014. **2**(5): p. 395-404.
12. Butler, C.C., et al., *Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial.* The Lancet, 2020. **395**(10217): p. 42-52.
13. Penttinen, P., et al., *Expert opinion on neuraminidase inhibitors for the prevention and treatment of influenza Review of recent systematic reviews and meta-analyses*. 2017: Stockholm.
14. Jackson, R.J., et al., *Oseltamivir, zanamivir and amantadine in the prevention of influenza: A systematic review.* Journal of Infection, 2011. **62**(1): p. 14-25.
15. Patrozou, E. and L.A. Mermel, *Does Influenza Transmission Occur from Asymptomatic Infection or Prior to Symptom Onset?* Public Health Reports, 2009. **124**(2): p. 193-196.
16. Gordon, A., et al., *Influenza Transmission Dynamics in Urban Households, Managua, Nicaragua, 2012–2014.* Emerging Infectious Disease journal, 2018. **24**(10): p. 1882-1882.
17. Moscona, A., *Neuraminidase Inhibitors for Influenza.* New England Journal of Medicine, 2005. **353**(13): p. 1363-1373.
18. Roche, *Tamiflu 75mg Hard Capsules SmPC*. 2018: Leatherhead, UK.
19. Dutkowski, R., et al., *Safety and Pharmacology of Oseltamivir in Clinical Use.* Drug Safety, 2003. **26**(11): p. 787-801.
20. Dutkowski, R., J.R. Smith, and B.E. Davies, *Safety and pharmacokinetics of oseltamivir at standard and high dosages.* International Journal of Antimicrobial Agents, 2010. **35**(5): p. 461-467.