Should we recommend neuroaminidase inhibitors for influenza?

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A recent Cochrane systematic review challenged the evidence base for neuraminidase inhibitors (NIs) by claiming that NIs have negligible efficacy in the treatment of influenza [1]. An individual patient data meta-analysis seemingly contradicts these findings [2]. The public, physicians, policy-makers and governments are now struggling to understand how to translate these findings to clinical practice.

Jefferson et al. [1] updated their Cochrane review of randomized controlled trials (RCTs) that compared NIs with placebo as treatment or prophylaxis for influenza, basing it on study reports sent to regulators in an attempt to include full data from all RCTs performed (60% of the data from RCTs on oseltamivir have not been published). The review included healthy children and adults of all ages, including people with chronic diseases that do not affect the immune system profoundly.

Among adults (eight trials, 3954 participants), oseltamivir reduced the duration of symptoms by 16.8 h (95% CI 8.4–25.1, no heterogeneity). Hospital admissions were identical in the placebo and NI treatment arms. Pneumonia rates were reported less frequently with treatment (numbers needed to treat (NNT) = 100), but the reduction was mainly observed in studies that did not collect this information systematically. Sinusitis and otitis media had the same rates. Nausea and vomiting were the most common adverse effects of the drug, but the rate of withdrawal because of adverse events was similar to that with placebo. The reduction in duration of symptoms for adults given zanamivir as inhalation or as nasal spray (13 studies, 5411 participants) was 14 h (95% CI 9–28 h, low heterogeneity). A significant reduction was observed in bronchitis rates, but not in pneumonia rates. Serious adverse events and adverse events that led to withdrawal from the study were not more common in the active arm than in the placebo arm.

When given for prophylaxis among adults and children, oseltamivir reduced the rate of symptomatic laboratory-confirmed influenza (relative risk (RR) 0.45 (95% CI 0.30–0.67, NNT c. 50), but not the rates of influenza-like illnesses, hospital admissions, or any other severe complication. Zanamivir reduced the rates of symptomatic influenza (RR 0.39, 95% CI 0.22–0.70, NNT c. 50) and pneumonia (RR 0.30, 95% CI 0.11–0.80, NNT 311). The rates of influenza-like illnesses were not available.

Elderly participants were separately investigated in only four prophylaxis trials. Few elderly patients were included in the treatment trials, and the Cochrane review did not assess this subgroup. The original studies did not include persons with severe underlying disorders or patients with a severe presentation of influenza, e.g. those requiring hospital admission.

Muthuri et al. [2], conducted an individual patient-data meta-analysis of observational studies, including 29 234 people from 78 centres (including our dataset [3]) hospitalized because of influenza A H1N1 (81.5% laboratory-confirmed). Patients given NIs had a lower fatality rate than patients not treated with NIs (adjusted OR 0.81, 95% CI 0.70–0.93). Patients given treatment within 2 days of symptom onset had a lower fatality rate than those given late treatment (adjusted OR 0.48, 95% CI 0.41–0.56). The meta-analysis shares two weaknesses with the observational studies published on this issue. Patients were not randomized to treatment vs. no treatment or to early vs. late treatment. Physicians had reasons for prescribing NIs in certain patients and for not prescribing them in others. We cannot be sure that the techniques used (adjusting for the propensity for treatment and risk factors for mortality) can compensate in full for this bias. Another potential source of bias is the immortal time bias: patients given treatment and late treatment survived at least to the day on which the treatment was prescribed. Researchers might have published positive results but not negative ones, and researchers showing positive results might have been more inclined to share their data and include them in the meta-analysis (publication bias). We also do not know whether the results obtained during the H1N1 pandemic can be generalized to all influenza epidemics or pandemics.

How should these data direct practice? For healthy people in the community, the modest reduction in symptom duration (out of the 7-day illness duration without treatment) with no other proven positive outcomes does not, in our opinion, justify treatment with NIs. In people admitted to hospital with severe influenza complications or severe
deterioration in underlying disorders related to influenza, treatment with NIs should be initiated early. National committees will face a difficult decision on whether continual stockpiling of NIs is justified, as pandemics are rare (and pandemics of severe disease even rarer) and cannot be predicted [4].

An RCT addressing patients sick enough to be hospitalized with influenza or suspected influenza is very unlikely. Given the results of the observational studies, weak as they are, and the relative safety of NIs, it is doubtful whether research ethics boards would approve such a study. For a long time, these are the data that we will have.

**Transparency Declaration**

None.

**References**


