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Factors associated with clinical and virological response in patients treated with oseltamivir or zanamivir for influenza A during the 2008–2009 winter

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Abstract

Oseltamivir or zanamivir are effective in outpatients with seasonal influenza; however, factors associated with response have been incompletely described. During the 2008/2009 epidemic, in a randomized trial for influenza A-infected outpatients, clinical (time to alleviation of flu-related symptoms) and virological (rate of patients with day 2 nasal viral load <200 cgeq/μL) responses to oseltamivir or zanamivir were assessed and associated factors were determined using multivariate analysis. For oseltamivir (141 patients) and zanamivir (149 patients) median times to alleviation of symptoms were 3 and 4 days, respectively; 59% and 34% had virological response. For oseltamivir, a lower clinical response was associated with female gender (HR, 0.53; 95% CI, 0.36–0.79), baseline symptoms score >14 (HR, 0.47; 0.32–0.70), viral load ≥5 log cgeq/μL (HR, 0.63; 0.43–0.93), and initiation of antibiotics (HR, 0.30; 0.12–0.76); a lower virological response was associated with female gender (OR, 0.45; 0.21–0.96), baseline viral load ≥5 log cgeq/μL (OR, 0.40; 0.20–0.84) and days 0–2 incomplete compliance (OR, 0.31; 0.10–0.98). For zanamivir, virological response was associated with age ≥50 years (OR, 0.29; 0.10–0.85) and initiation of antibiotics at baseline (OR, 4.24; 1.07–17.50). Factors associated with lower response to neuraminidase inhibitors in outpatients appeared to be easily identifiable during routine clinical examination and, when appropriate, by nasal sampling at baseline. The unknown association between gender and response to oseltamivir was not explained by compliance.

Keywords: Epidemiological factors, gender, neuraminidase inhibitors, seasonal influenza, treatment outcome
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Introduction

In influenza-infected patients, recent systematic reviews have shown that neuraminidase inhibitors reduce the median time of symptom alleviation in adults and children by approximately 0.5 day [1–3]. Beyond reducing the duration of the disease, antivirals have a variable impact on reducing the viral nasal shedding [4–7].

In 2009 for pandemic A(H1N1) influenza, the World Health Organization recommended the use of neuraminidase inhibitors, oseltamivir or zanamivir, for the treatment of patients with confirmed or strongly suspected influenza infection, when clinical presentation was severe or for patients in higher risk groups [8]. However, factors influencing the clinical and virological responses, which may help physicians to detect patients who will get the lowest benefit from treatment and have to be particularly followed-up, have

been incompletely analysed. Several factors associated with the clinical response in patients receiving oseltamivir were identified in a few studies as: age, high body temperature, delay from onset to treatment start, influenza virus type and infection with an oseltamivir-resistant A(H1N1) virus [9–13]. No specific study has been conducted to evaluate factors influencing the response to zanamivir.

To address these questions, we analysed the data from a double-blind randomized controlled trial performed during seasonal influenza. This trial (Bivir) conducted in France during the A(H3N2) 2008/2009 epidemic, compared the effectiveness of an oseltamivir-zanamivir combination with each of the monotherapies plus placebo. As this trial found an oseltamivir-zanamivir combination to be less effective than oseltamivir monotherapy [14], we chose to analyse data collected only from patients treated with a WHO recommended regimen (i.e. oseltamivir or zanamivir monotherapy). A better understanding of these factors influencing response to neuraminidase inhibitors would provide important insights into the use of antivirals in future seasonal epidemics or pandemics.

Methods

Recruitment and follow-up of participants

The present study is a secondary analysis of data collected in the Bivir trial, a community-based randomized trial, conducted between 7 January and 15 March 2009 (period of the influenza epidemic in France during the winter 2008–2009), reported in detail elsewhere [14]. Briefly, patients were adults over 18 years old who consulted their general practitioner within 36 h of onset of influenza symptoms and had a positive nasal rapid test for influenza A. Exclusion criteria were: vaccination against influenza during the 2008–2009 season; recent exacerbation of COPD; previous history of depression; and known hypersensitivity to neuraminidase inhibitors. Patients gave informed written consent to participate in the study. The protocol was approved by the Ethics Committee of Ile de France 1.

At enrollment (day 0), a nasal swab for virological analysis was performed by the general practitioner before initiation of treatment. In the present study, only day 0 PCR documented influenza A-infected patients, allocated to one of the two oseltamivir or zanamivir monotherapy arms out of three arms of the Bivir trial, were analysed. Oseltamivir (Roche, Bale, Switzerland) dosage was 75 mg orally twice daily; zanamivir dosage was 10 mg by oral inhalation using the commercialized GlaxoSmithKline Diskhaler® (GlaxoSmithKline, Philadelphia, PN, USA), twice daily. The first drug administration was performed in the presence of the general practitioner after the patient had been given instructions on capsule intake and diskhaler use. Treatments were thereafter self-administered twice daily for 5 days. A self-administered questionnaire was given to the patient for self-evaluation of symptoms and notification of drug intake twice daily. A nurse visited the patients on day 2, performed a nasal swab for virological analysis between the 4th and 5th drug intake, and collected data on any adverse event. Patients returned to their general practitioner 2 days (day 7) after completion of treatment for follow-up examination and to report any adverse event. Patients were also contacted by phone on day 14 to collect data on any further adverse events.

Statistical analysis

As in the main analysis of the Bivir trial [14], clinical response was assessed as the time to alleviation of influenza-related symptoms and virological response as the rate of patients with, at day 2, a normalized nasal viral load determined by RT-PCR below 200 cgeq/μL [14].

Factors associated with clinical or virological response were studied separately for oseltamivir and zanamivir by performing univariate and then multivariate analysis, using Cox regression for the clinical response and logistic regression for virological response. The following explanatory variables were studied: gender, age, smoking status, delay from onset of any symptom and start of treatment, baseline symptoms score, baseline fever, baseline physical signs (defined as conjunctival hyperaemia, erythematous throat, congestive eardrum, abnormal chest auscultation, or other), presence at baseline of at least one co-morbidity, or one clinical complication, or initiation of antibiotics, type of influenza virus, baseline normalized viral load, and full compliance between day 0 and day 2 (defined as having perfectly taken up the prescribed treatment during the first 2 days of the trial).

From the univariate analyses results, a multivariate model was built with all variables with p-values <0.10 and then a backward selection approach was used. Then, for each clinical or virological response outcome, a model with all variables remaining in the model either for oseltamivir or for zanamivir, was constructed in order to compare the results of the two drugs with similar adjustments. All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Clinical and virological responses were assessed, respectively, in the 141 and 149 influenza A-infected outpatients random-