Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial

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We conducted a double-blind, randomized trial of 134 outpatients with polymerase chain reaction-confirmed influenza to assess the effects of oseltamivir initiated 48–119 hours after illness onset. Oseltamivir treatment did not reduce illness duration, severity, or duration of virus detection. However, the power of this study was limited due to lower than expected enrollment.

Keywords. influenza; oseltamivir.

Neuraminidase inhibitors (eg, oseltamivir) will be an important countermeasure prior to vaccine availability during a pandemic. Most studies suggest that oseltamivir is most effective if initiated <48 hours after illness onset; early treatment mitigates severity and reduces illness duration by 1–3 days [1–5]. Drug delivery logistics will be challenging during a pandemic; initiating treatment <48 hours may not be possible.

We conducted a double-blind, randomized, placebo-controlled trial during 4 influenza seasons: 2007–2008 through 2010–2011 to assess duration of influenza symptoms and viral shedding in outpatients who initiated late oseltamivir therapy (48–119 hours after illness onset). Currently, antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who is hospitalized or at higher risk for influenza complications [6].

METHODS

Patients aged 1–79 years were prospectively recruited at the Marshfield Clinic in Marshfield, Wisconsin, if they sought medical attention for acute respiratory illness during the influenza season. Patients were eligible for influenza testing if they reported feverishness, chills, or cough <120 hours (5 days) in duration. Before participation, patients were evaluated by a healthcare provider with no connection to the study. For ethical reasons, study participation was restricted to patients who were evaluated and not prescribed antiviral therapy.

After written informed consent was provided, a research coordinator collected a nasal or nasopharyngeal swab for influenza testing by rapid antigen test (during 2007–2008) and/or real-time reverse-transcription polymerase chain reaction (RT-PCR) (all seasons). Reverse-transcription PCR was performed locally using the Centers for Disease Control and Prevention’s primers and probes [7]. Rapid test and RT-PCR results were usually available within 4 and 24 hours, respectively. Positive rapid tests were confirmed by RT-PCR. Patients were randomized to receive oseltamivir or placebo in a 2:1 ratio, and treatment was initiated as soon as possible after the initial positive result.

Persons >88 pounds received a 75 mg oseltamivir or identical placebo capsule twice daily for 5 days (10 doses). Children ≤88 pounds received a liquid form of oseltamivir at a concentration of 15 mg/mL or placebo at the standard dose for weight. Separate randomization tables were used for capsule and suspension formulations, and sequential numbers were randomly assigned to active drug or placebo in blocks of 6. Study drugs were prepared in advance according to the randomization table and prelabeled with the sequential randomization number. Compliance was monitored by asking participants to report each dose taken when completing symptom reports, described below.

Additional swabs were collected immediately before (day 0) and on day 3 or 4 after study drug initiation. Few participants were culture positive; therefore, we used RT-PCR detection to approximate viral shedding, recognizing that viral nucleic acid may be detectable in the absence of infectious virus.

Each randomized participant (or guardian) completed a symptom survey every morning and evening by telephone or securely online. Reporting continued for at least 7 days after initiation of study drug or until symptoms had resolved (up to 14 days). Participants received a digital oral thermometer and were instructed to measure and record their temperature in the
morning and evening. For each reporting period, participants reported symptoms of feverishness, cough, fatigue, nasal congestion, wheezing, headache, muscle aches, and sore throat on a scale from 0 (absent) to 3 (severe). Symptom scores ranged from 0 (all symptoms absent) to 24 (all symptoms severe). Headache, sore throat, and muscle aches were not assessed for children aged <24 months because parents could not reliably identify those symptoms. Use of decongestants, antitussives, or antipyretics was reported daily.

The study was originally funded for a 2-year period (2007–2008 and 2008–2009) with the intent to enroll and randomize 525 patients. This sample size was estimated to provide 80% power to detect a reduction of 0.6 days in duration of illness compared with placebo recipients who initiated treatment 48–119 hours after illness onset. Due to unforeseen events, recruitment was extended over 4 seasons and the target sample size was not achieved. In the second season (2008–2009), enrollment was suspended in February due to high prevalence of oseltamivir-resistant influenza viruses. Enrollments from 2008 to 2009 were excluded from this analysis, and descriptive results were published separately [8]. In 2009–2010, the H1N1 pandemic occurred in October–November before the study was ready to enroll participants; influenza was nearly absent after study enrollment began in early December. In 2010–2011, enrollment was suspended mid-season due to the expiration of funding. This study was approved by the Institutional Review Board at Marshfield Clinic and registered at clinicaltrials.gov (NCT00555893).

Intention-to-treat analysis was used to assess the results among participants with RT-PCR-confirmed influenza who were randomly assigned a treatment group <120 hours after illness onset, took ≥1 dose of the assigned medication, and completed ≥1 symptom survey. All analyses were specified before unmasking and stratified based on randomization/drug initiation relative to illness duration: early treatment (illness duration <48 hours) and late treatment (illness duration 48–119 hours). Kaplan-Meier analyses were conducted to examine time to symptom resolution and PCR positivity at day 3–4 postrandomization. Symptom resolution was defined as occurring at the start of the first 24-hour period in which the total symptom score was ≤2 with no symptom rated higher than mild (symptom score of ≤1). The definition of symptom resolution was modified slightly, before analysis, from the original protocol, which did not consider the total symptom score. Time to resolution was calculated from the time of randomization to symptom resolution in 12-hour increments. Survival curves for each treatment group were compared using log-rank tests, and comparisons of survival at specific time points were undertaken using methods described by Klein and Moeschberger [9]. Events were censored at the last reported survey period or 14 days after randomization, whichever came first.

Specimens for PCR testing after randomization were not available for some participants (n = 16), and some (n = 4) had provided specimens multiple times between randomization and day 3–4 postrandomization. To evaluate virus detection in the 2 treatment groups, we examined the estimated probability of RT-PCR positivity on day 3–4 after randomization. Participants were assigned a time-to-event value of 3.5 if they had a negative (failed) or positive (censored) PCR result on day 3 or 4. The probability of PCR positivity at day 3–4 was calculated based on the survival function at time 3.5.

The effect of treatment on subjective symptom severity was assessed using a maximum and mean severity score. Mean severity score was calculated for each participant by summing

### Table 1. Outcomes by Treatment Group and Illness Duration at the Time of Treatment Initiation

| Outcome                                              | Placebo          | Drug            | P Value |
|------------------------------------------------------|------------------|-----------------|---------|
| Late treatment (48–119 hours)                         |                  |                 |         |
| Time from treatment initiation to symptom resolution, median days (95% CI) | 4 (3.5, 5)       | 4 (3.5, 5)      | .5      |
| Probability of symptom resolution on day 3–4 of treatment (95% CI) | 0.32 (0.17, 0.46) | 0.37 (0.27, 0.47) | .5      |
| Probability of symptom resolution on day 7 of treatment (95% CI) | 0.66 (0.74, 0.97) | 0.81 (0.73, 0.89) | .6      |
| Probability of positive RT-PCR on day 3–4 of treatment (95% CI) | 0.11 (0.01, 0.21) | 0.13 (0.06, 0.20) | .8      |
| Mean severity score*, median (IQR)                   | 5.7 (2.5, 4.8)   | 6.1 (4.9, 7.7)  | .5      |
| Maximum severity score*, median (IQR)                | 11.5 (8, 14)     | 12 (9, 15)      | .2      |
| Early and late treatment (<120 hours)                |                  |                 |         |
| Time from treatment initiation to symptom resolution, median days (95% CI) | 4 (3.5, 4.5) | 4 (3.5, 5) | .4      |
| Probability of symptom resolution on day 3–4 of treatment (95% CI) | 0.35 (0.21, 0.48) | 0.39 (0.30, 0.48) | .6      |
| Probability of symptom resolution on day 7 of treatment (95% CI) | 0.89 (0.80, 0.98) | 0.82 (0.75, 0.89) | .2      |
| Probability of positive RT-PCR on day 3–4 of treatment (95% CI) | 0.15 (0.05, 0.25) | 0.18 (0.10, 0.25) | .6      |
| Mean severity score*, median (IQR)                   | 5.8 (4.8, 7.7)   | 6.1 (5.0, 7.7)  | .6      |
| Maximum severity score*, median (IQR)                | 11.5 (7.5, 14)   | 12 (10, 15)     | .2      |

Abbreviations: CI, confidence interval; IQR, interquartile range; RT-PCR, reverse-transcription polymerase chain reaction.

*Patients aged ≥24 month, highest possible severity score was 24.
the symptom severity scores for all reporting periods from randomization through the first period of symptom resolution, divided by the number of reporting periods. Children aged <24 months (n = 5) were excluded from the analysis of illness severity because they were not asked to report all symptoms.

RESULTS

We enrolled and randomized 193 patients with RT-PCR-confirmed influenza (Supplementary Figure 1). Twenty-eight patients who initiated treatment ≥120 hours after illness onset were excluded. Influenza A and B was detected in 123 and 41 patients, respectively; 1 patient was positive for both types. The distribution of early and late treatment groups was determined by the patient’s healthcare-seeking behavior and the time to confirm influenza. There were 134 patients who were randomized and initiated treatment 48–119 hours after illness onset (late treatment group). Of these, 95 received oseltamivir and 39 received placebo. Thirty-one patients initiated treatment <48 hours after illness onset (early treatment group); 19 received oseltamivir and 12 received placebo.

Within the late treatment group, oseltamivir and placebo recipients were similar with respect to age, sex, duration of illness, and symptom severity score at randomization (Supplementary Table 1). There were no differences between treatment groups with regard to symptom resolution, duration of virus detection, and severity of illness (Table 1). The probability of resolution by day 3 postrandomization was 0.37 (95% confidence interval [CI], 0.27–0.47) for patients who received oseltamivir and 0.32 (95% CI, 0.17–0.46) for patients who received placebo (P = .5). The probability that patients were RT-PCR positive through day 3–4 postrandomization was 0.13 (95% CI, 0.06–0.20) and 0.11 (95% CI, 0.01–0.21) for patients who received oseltamivir and placebo, respectively (P = .8) (Supplementary Figure 2). The mean and maximum severity scores were similar in the oseltamivir and placebo group. Similar results were observed when all patients randomized <120 hours of illness onset were included.

DISCUSSION

There are few therapeutic options for influenza, and antiviral therapy remains a critical intervention for both seasonal and pandemic infections. In this study, late treatment with oseltamivir did not reduce duration or severity of symptoms or RT-PCR-positive results on day 3–4. However, this study was underpowered due to unexpected circumstances. A clinical trial in Bangladesh, enrolling mostly children, found that oseltamivir treatment initiated ≥48 hours significantly decreased symptom duration, although the median days of illness was the same between the placebo/oseltamivir groups unless restricted to those persons treated on day 3 since illness onset (median 4 days for placebo and 3 days of oseltamivir). In addition, they showed that virus detection and isolation were significantly lower in the oseltamivir group on days 2 and 4 [10]. Together, these studies suggest that for uncomplicated influenza treated in ambulatory settings, late oseltamivir initiation has a minimal effect on symptoms.

Supplementary Material

Supplementary material is available online at Open Forum Infectious Diseases (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

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