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Effectiveness of a new bioequivalent formulation of oseltamivir (Enfluvir®) on 2010–2011 seasonal influenza viruses: an open phase IV study

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SUMMARY

Objective: The aim of this multicenter prospective study was to evaluate the efficacy of a new bioequivalent formulation of oseltamivir for the treatment of influenza A, influenza B, and H1N1 during the 2010–2011 influenza season.
Methods: We compared the symptoms and signs of 300 pediatric patients presenting to three university hospitals with an influenza-like illness between January and March 2011. Nasal swab specimens were collected from all children and tested by reverse-transcription polymerase chain reaction (RT-PCR) for influenza viruses. After randomization, half of the participants were prescribed oseltamivir, while the other half were observed conservatively. Forty patients who were followed-up for influenza prior to the study were also included in the evaluation.
Results: Influenza was confirmed by RT-PCR in 129 children, 71 of whom were prescribed oseltamivir. The durations of the symptoms fever, cough, nasal congestion, and rhinorrhea were significantly shorter for patients who were treated with oseltamivir compared with untreated patients ($p < 0.002$ for all symptoms). Early initiation of oseltamivir therapy (within 48 h of the onset of symptoms) was associated with more favorable outcomes and an earlier recovery than in patients for whom treatment was delayed (beyond 48 h). Thirty-seven patients (28.7%) had H1N1, 44 (34.1%) had influenza A, 46 (35.7%) had influenza B, one (0.8%) had H1N1 plus influenza A, and one (0.8%) had influenza A plus influenza B viruses. In the comparison of the duration of symptoms according to the different virus types, a statistically significant difference was only observed in patients with influenza B who had a longer duration of cough ($p < 0.001$), nasal congestion ($p < 0.001$), and rhinorrhea ($p < 0.001$).
Conclusions: Oseltamivir is an effective treatment for the management of seasonal influenza and H1N1, and should be initiated immediately without waiting for laboratory confirmation of diagnosis.

1. Introduction

Influenza is a major threat worldwide, resulting in severe illness and deaths each year, and is caused by the circulation of influenza viruses that are ubiquitous in the population. Each year, during the influenza season, the viruses spread rapidly, with 5–20% of the population reported to be infected by influenza viruses. In the USA alone, an estimated annual average of 36 000 deaths and 1 200 000 hospitalizations are attributable to influenza virus infections,[1,2] with similar rates reported in Europe and Asia.[3,4]

Infections with seasonal viruses tend to be more severe and progress more rapidly in young infants, the elderly, and those with an immunodeficiency, cardiopulmonary disease, pregnancy, or other chronic illnesses.[5,6] These patient groups are considered to be at high risk for influenza-associated complications, which include sinusitis, otitis media, croup, bronchitis, and pneumonia.[2]

Antiviral drugs used in the treatment of seasonal influenza accelerate the decline in viral load, shorten the duration of viral shedding, and reduce the length of hospital stay,[7] while also decreasing the risk of death.[8,9] The US Centers for Disease Control

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and Prevention (CDC) recommend antiviral therapy with neuraminidase inhibitors such as oseltamivir and zanamivir (rather than amantadine or rimantadine) for the treatment of seasonal influenza in individuals presenting to medical care with symptoms of less than 48-h duration.[1] Oseltamivir has been the most widely used drug in clinical practice, with more than 65 million prescriptions worldwide.

Potential influenza cases can be identified based on clinical signs and symptoms suggestive of influenza, without the need for laboratory confirmation. These influenza-like symptoms have been shown to be more specific when making a diagnosis of influenza during an epidemic.[10]

Seasonal influenza is associated with significant morbidity and mortality in the pediatric population, as well as placing a heavy burden on health costs due to substantial use of hospital resources.[11–13] School-age children are an important source for the spread of the influenza virus, with reported attack rates of more than 40% in preschool children and 30% in school children during influenza epidemics. The socioeconomic impact of pediatric influenza on children and other household members is substantial.[14,15]

In this study, a group of children who presented with influenza-like symptoms were treated with oseltamivir, and comparisons were made with patients who were treated conservatively in terms of duration of symptoms as well as efficacy of and response to treatment. Oseltamivir has been used in capsule form (Tamiflu®) and as an oral suspension (Tamiflu®) in Turkey for several years. Since Tamiflu has been the only oseltamivir preparation in our country and its use increased during the recent influenza pandemic, there have been problems in the supply of this drug. Oseltamivir has been made available and licensed for the therapy and prevention of pediatric influenza in Turkey as an oral suspension under the name Enfluvir®. This study was planned to determine the effectiveness of this new formulation in pediatric patients with influenza. In addition, the presence and subtypes of influenza viruses encountered in the 2010–2011 influenza season were determined, and differences in clinical presentations were investigated.

2. Methods

2.1. Study population and design

This prospective multicenter study of patients presenting to the pediatric outpatient clinics and the emergency departments of three university hospitals in Turkey, namely Hacettepe University, Çukurova University, and Ege University, was undertaken between January and March 2011.

Children aged ≤18 years presenting with influenza-like illness during the study period were enrolled in the study after parental consent was obtained. A broad definition of acute respiratory illness was used to identify patients who had potentially contracted influenza: the presence of two or more signs or symptoms (temperature ≥37.8 °C, cough, headache, sore throat, myalgia, congestion, and rhinorrhea) with a duration of one or more days during follow-up, as defined in previous studies.[16] The surveillance definition for influenza-like illness recommended by the CDC (temperature ≥37.8 °C plus cough or sore throat) was also used.[17] An influenza surveillance questionnaire was completed for each patient to obtain information on patient age, influenza vaccination status, beginning and end of symptoms, presence of complications, use of medications (antipyretics, antibiotics, antivirals, etc.), need for hospitalization, and the presence of an underlying chronic disorder.

2.2. Laboratory tests

Nasal swab specimens were collected from all children who presented with influenza-like symptoms. The specimen was obtained from a depth of 2–3 cm using a sterile cotton swab inserted into the nostril and was then inoculated into a vial containing M4 viral transport medium (Medical Wire & Equipment, UK). Swabs were stored at room temperature and transported to the Virology Laboratory of Istanbul University to be tested for seasonal influenza viruses by reverse-transcription polymerase chain reaction (RT-PCR) within 72 h of collection. The standard operating protocol as defined by the CDC was adhered to throughout this process.

After nasal swabs were obtained, patients were randomized and assigned to either the oseltamivir treatment group or the untreated group. Doses were set based on CDC recommendations. For children less than 1 year of age, oseltamivir was given at a dose of 3 mg/kg twice daily. Older children were prescribed the drug at doses adjusted to their weight: ≤15 kg, 30 mg twice a day; 15–23 kg, 45 mg twice a day; 24–40 kg, 60 mg twice a day; >40 kg, 75 mg twice a day.

A standard protocol was followed at all three centers, which required participants to attend follow-up visits on the third, fifth, and tenth day of treatment, with the aim of ensuring patient compliance and to monitor side effects and the duration of symptoms. Patients/parents were asked to measure body temperature at least three times a day. A patient was considered afebrile when his/her body temperature remained <37.5 °C for more than 24 h without the use of antipyretics. The highest body temperature during the course of the disease was also recorded. Time to resolution of symptoms that were present on first presentation (e.g., cough, sore throat, myalgia, congestion and rhinorrhea, vomiting, and diarrhea) was also noted. For patients who could not be brought to the hospital, parents were contacted by phone.

The study was approved by the institutional review boards at the University of Hacettepe. Informed consent was obtained from the parent or legal guardian of each participant, and participants aged ≥6 years completed assent procedures.

2.3. Statistical analysis

Statistical analyses were performed using Stata version 15.0 (Stata Corp., College Station, TX, USA) and the *R* statistical package (version 2.10.1). Comparisons of proportions between the groups were done by the standard Chi-square test and Fisher's exact test. The Mann–Whitney *U*-test and Kruskal–Wallis one-way analysis of variance according to rank were used to compare nonparametric continuous data between the groups. The bivariate Spearman correlation test was used to examine the strength of association between the starting time of oseltamivir and duration of symptoms. A *p*-value of less than 0.05 was considered to be indicative of statistical significance.

3. Results

3.1. Demographic characteristics

During the period from January through March 2011, a total of 300 patients with influenza-like illness were evaluated. The median age of patients was 36 months (interquartile range 2–204 months) and 55% were male. Of the 300 patients, none had a chronic disorder such as asthma, or a chronic pulmonary or cardiac disease. Forty-five of the three-hundred patients (15%) included in the study had been vaccinated with the seasonal influenza vaccine before presenting to our hospital.

Table 1
Comparison of the duration of symptoms between RT-PCR positive and negative patients presenting with influenza-like symptoms

Parameter	RT-PCR-positive (n)[a]	RT-PCR-negative (n)[a]	p-Value
Fever	4.56 ± 2.56 (126)	3.88 ± 1.60 (129)	0.024
Cough	6.79 ± 3.51 (112)	6.08 ± 3.13 (136)	0.056
Nasal congestion	5.61 ± 3.21 (113)	5.41 ± 2.81 (141)	0.418
Rhinorrhea	5.53 ± 3.16 (115)	5.53 ± 2.81 (130)	0.983
Sore throat	3.15 ± 1.18 (40)	3.51 ± 1.36 (56)	0.618
Myalgia	5.50 ± 2.33 (31)	3.74 ± 2.01 (16)	0.02
Headache	4.54 ± 3.26 (30)	3.83 ± 2.40 (33)	0.518
Breathing difficulties	2.57 ± 1.39 (7)	2.36 ± 1.43 (11)	0.696

[a] Results are mean ± standard deviation days (number of patients with the symptom).

3.2. Clinical symptoms and laboratory findings

The most common symptoms on first presentation were fever (262/300, 87.3%), cough (254/300, 84.7%), nasal congestion (259/300, 86.3%), rhinorrhea (251/300, 83.7%), sore throat (96/300, 32%), headache (64/300, 21.3%), and myalgia (49/300, 16.3%). Only 8.7% (26/300) of patients reported gastrointestinal tract symptoms such as nausea, vomiting, or diarrhea. Lower respiratory tract findings were respiratory distress in 18.6%, crepitations in 5.3%, and wheezing in 3.1%. Physical findings on presentation were consistent with acute otitis media in seven patients (2.3%), acute bronchiolitis in three patients (1%), and acute sinusitis in one patient (0.3%). Neurological symptoms (febrile convulsion, encephalopathy, etc.) were present in four patients (1.3%) at presentation.

With regard to drug use before presentation, 275 patients (91.7%) had used antipyretics, while 103 patients (34.3%) reported antibiotic use. The most commonly used antipyretic was paracetamol (82%), and amoxicillin–clavulanic acid was the most frequently used antibiotic (78%). Thirteen patients (4.3%) were hospitalized due to breathing difficulties, feeding problems, and deterioration of general condition, although none of them required observation in the intensive care unit.

At least one influenza virus was detected in 129 (43%) patients using the RT-PCR method. One hundred and sixty-four (54.7%) samples were negative and seven (2.3%) swabs were deemed inadequate.

When RT-PCR positive and negative patients were compared in terms of duration of symptoms, RT-PCR-positive patients had significantly longer periods of fever ($p < 0.05$) and myalgia ($p < 0.05$). Although the duration of cough was longer in the RT-PCR-positive group, the difference was not statistically significant ($p = 0.056$) (Table 1).

3.3. Treatment and clinical course

After randomization, half of the participants were prescribed oseltamivir, while the other half were observed conservatively. Findings were compared with those of 40 patients who were followed-up for influenza prior to the study. Oseltamivir was prescribed for 129 (43%) patients, while 171 (57%) patients remained untreated with an antiviral agent. Figure 1 depicts the study assignment and follow-up. The durations of fever, cough, nasal congestion, and rhinorrhea from onset were significantly shorter in seasonal influenza patients who were treated with oseltamivir than in those who were not treated (for all four symptoms, $p < 0.002$). The frequency and duration of symptoms in both groups are summarized in Table 2.

In the treated group, 55 patients (43.7%) had a positive RT-PCR compared to 71 patients (56.3%) who were RT-PCR-negative. Of the 129 patients with a confirmed influenza infection, 71 (55.0%) were

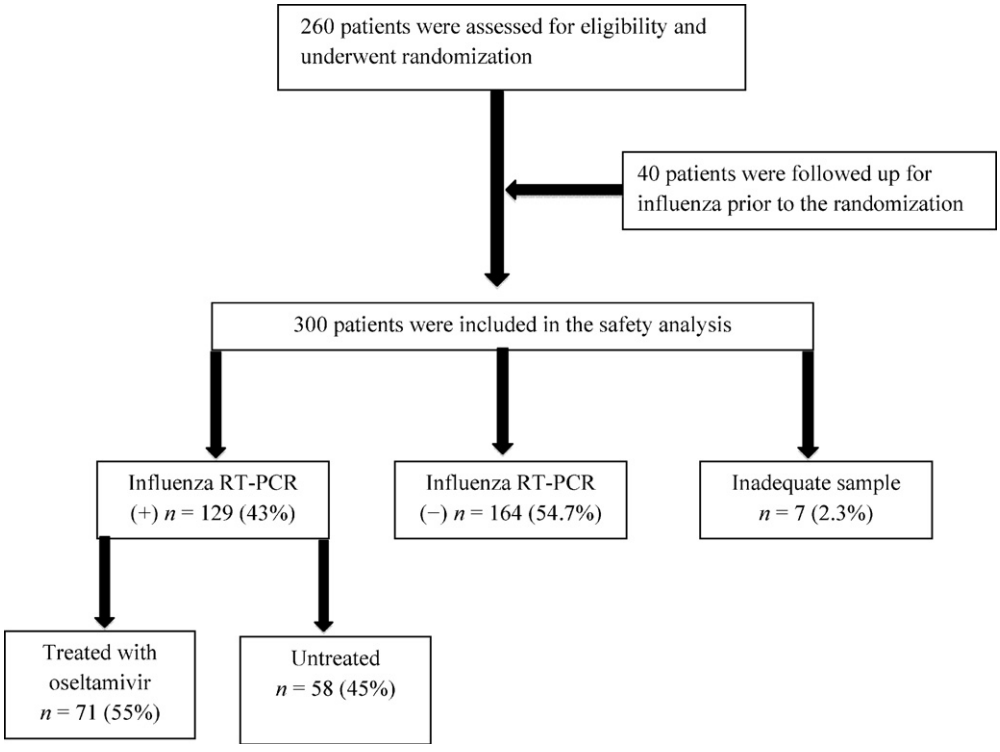

Figure 1. Study assignment and follow-up.

Table 2
Duration of symptoms in oseltamivir treated and untreated RT-PCR-positive influenza patients

Parameter	Oseltamivir treated (n)[a]	Untreated (n)[a]	p-Value
Fever	3.76 ± 2.27 (69)	5.52 ± 2.59 (57)	0.000
Cough	6.28 ± 3.78 (63)	7.44 ± 3.04 (49)	0.002
Nasal congestion	5.16 ± 3.39 (62)	6.17 ± 1.26 (51)	0.001
Rhinorrhea	5.01 ± 3.16 (68)	6.27 ± 3.04 (47)	0.001
Sore throat	2.98 ± 1.21 (22)	3.01 ± 1.28 (18)	0.678
Myalgia	3.72 ± 2.16 (18)	3.76 ± 1.87 (13)	0.665
Headache	3.95 ± 2.83 (20)	3.60 ± 1.26 (10)	0.734

[a] Results are mean ± standard deviation days (number of patients with the symptom).

treated with oseltamivir while 58 (45.0%) were untreated. No severe adverse reactions were reported in association with the drug.

The effect of oseltamivir on the duration of symptoms was evaluated based on the duration between the onset of symptoms and initiation of the treatment. Duration of symptoms such as fever ($p < 0.001$, $R = 0.373$), cough ($p < 0.001$, $R = 0.470$), nasal congestion ($p < 0.001$, $R = 0.348$), and rhinorrhea ($p < 0.001$, $R = 0.401$) were significantly longer in patients for whom treatment was delayed (>48 h). The use of an antibiotic prior to oseltamivir treatment did not have a statistically significant effect on the duration of symptoms.

With regard to the distribution of influenza virus types/subtypes in patients with a positive RT-PCR, 37 patients (28.7%) had H1N1, 44 (34.1%) had influenza A, 46 (35.7%) had influenza B, one (0.8%) had H1N1 plus influenza A, and one (0.8%) had influenza A plus influenza B. In terms of duration of symptoms, a statistically significant difference was only observed in patients with influenza B who had a longer duration of cough ($p < 0.001$), nasal congestion ($p < 0.001$), and rhinorrhea ($p < 0.001$). Figure 2 depicts the frequency of symptoms according to type/subtype of influenza virus.

Among the 45 patients who had previously been vaccinated with the seasonal influenza vaccine, 33 (73.3%) had a negative RT-PCR result, five (11.1%) had confirmed influenza A, five (11.1%) had influenza B, and two were positive for H1N1.

Of the patients who presented with acute otitis media, three were positive for H1N1, two were positive for influenza B, and one was positive for influenza A. Only one patient had a negative RT-PCR result. The only patient with acute sinusitis had H1N1. Out of the three patients with febrile convulsions, one had H1N1, one had influenza B, while one patient had a negative RT-PCR result. The patient who developed encephalopathy had influenza B.

Gastrointestinal symptoms were present in 18 (14%) patients who were influenza-positive; seven had influenza A, six had influenza B, and five had H1N1.

RT-PCR was positive in five of the 13 patients who were hospitalized, three of whom had influenza B and two had H1N1. The hospitalization rate was not significantly different between the RT-PCR positive and negative groups. The overall hospitalization rate for patients with a confirmed influenza infection was 3.8%. Tachypnea and breathing difficulties were the indications for hospitalization in three patients, whereas one patient was admitted due to feeding problems as a result of nausea and vomiting. One patient was hospitalized after developing encephalopathy.

4. Discussion

Early administration of oral oseltamivir has been reported to be associated with earlier resolution of symptoms in patients with influenza. Several large prospective studies in pediatric and adult patients have clearly shown that antiviral therapy reduces the duration of symptomatic illness by up to 2 days if started within 48 h of the onset of symptoms.[18,19] In one trial, children aged 1–12 years with influenza-like illness of <48 h duration received either oseltamivir or placebo twice daily for 5 days.[20] Compared with placebo, oseltamivir significantly reduced symptom duration in those with laboratory-confirmed influenza ($n = 452$) by 36 h ($p < 0.0001$), while also decreasing the extent and severity of illness by 29% ($p = 0.002$). In our study on children with confirmed influenza, a new syrup formulation of oseltamivir therapy resulted in a significant reduction in the mean time to resolution of fever from 5.52 days to 3.76 days ($p = 0.000$), cough from 7.44 days to 6.28 days ($p = 0.002$), nasal congestion from 6.17 days to 5.16 days ($p = 0.001$), and rhinorrhea from 6.27 days to 5.01 days ($p = 0.001$).

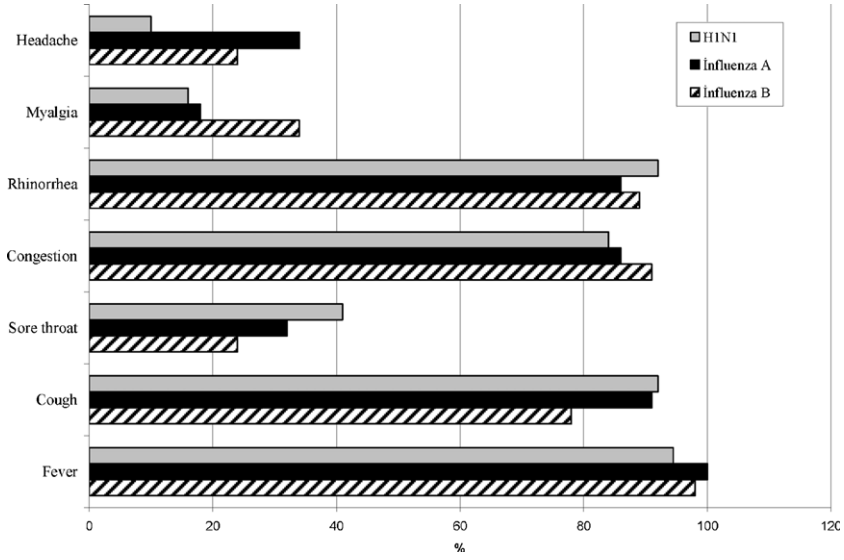

Figure 2. Frequency of symptoms according to type/subtype of influenza virus.

Current guidelines recommend immediate antiviral treatment in patients with a suspected influenza infection, without waiting for laboratory confirmation of the diagnosis,[21] citing that the earlier these drugs are started, the better the clinical outcome.[18] The replication of influenza viruses peaks at 24–72 h after the onset of symptoms, and the viral load correlates positively with the severity of symptoms.[18,22,23] Based on our knowledge, early administration of oseltamivir would be expected to provide the greatest clinical benefit. This is also supported by our study results.

Fever was clearly the most prominent sign of influenza, as has been reported previously by other investigators.[24] However, a recent meta-analysis revealed that fever occurred in only one-third of healthy participants who were exposed to an experimental seasonal influenza virus infection.[25] Only 2.3% of children in the influenza-positive group were afebrile in our study. In uncomplicated seasonal influenza, illness typically resolves within 3–7 days.[1] In our influenza-positive patient group, symptoms resolved after 1.5–8 days, with oseltamivir treatment associated with a mean duration of fever of 1.7 days.

Treatment with oseltamivir also resulted in significant reductions in the duration of cough,[26] with an observed mean duration of reduction of 1.2 days. Similar reductions in the durations of nasal congestion (1 day) and rhinorrhea (1.2 days) were also observed.

When we look at the clinical severity and complications, we see that gastrointestinal symptoms were documented in only 14.0% of the RT-PCR-positive children in our study. However, they have been reported to occur in approximately one-third of children with influenza.[27,28] In our study, 4.7% of RT-PCR-positive children had acute otitis media at their first visit, a rate much lower than those reported in previous studies.[29,30]

Neurological dysfunction is an important complication of influenza infections,[31] with reported cases of encephalopathy,[32] febrile seizure,[33] Reye's syndrome,[34] and encephalitis lethargica.[35] Febrile seizure is by far the most common neurological complication, with reported rates of more than 20% in children hospitalized for influenza.[34] The neurological complication rate in our RT-PCR-positive study population was 2.3% and most of them were febrile seizures.

Treatment with oseltamivir has been shown to decrease the use of antibiotics in children with influenza by 10% ($p = 0.03$).[26,36] However, we could not demonstrate similar reductions in our study population. This may be related to the low rate of complications in our patients. Our hospitalization rate was 3.9% in patients with confirmed influenza, all of whom were younger than 5 years of age with a mean age of 34 months. Hospitalization rates in the USA were highest in this age group according to a summary report published by the CDC on influenza activity covering the period between October 3, 2010 and February 5, 2011.[37]

In our study, patients infected with influenza B had significantly longer durations of the symptoms cough, nasal congestion, and rhinorrhea, compared to those positive for influenza A (H1N1 and unspecified subtypes). In comparison to seasonal influenza, pandemic H1N1 has been shown to be associated with a significantly higher rate of symptoms in children presenting with flu-like symptoms ($p < 0.05$).[38] A recent study also demonstrated a weaker response to oseltamivir therapy in patients infected with influenza B compared to influenza A, with the influenza B virus being isolated more frequently than the influenza A virus following treatment with oseltamivir.

In conclusion, oseltamivir therapy is associated with significant reductions in the duration of symptoms, and should be considered in all patients thought to be at high risk for developing severe complications. We strongly recommend early initiation of antiviral therapy without waiting for laboratory confirmation of the diagnosis.

Conflict of interest: None.

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