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ORIGINAL ARTICLE

Impact of oseltamivir use on the reduction of complications in patients with influenza: a prospective study

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Abstract To evaluate the factors associated with oseltamivir prescription and to study the effectiveness of oseltamivir in reducing influenza-related complications. A prospective cohort study using the SOS Doctors (a network of physicians who perform house-call visits in Attica, Greece). Patients with confirmed or clinically suspected influenza were followed up to 14 days during the 2011-2012 influenza period. 410 patients with confirmed or suspected influenza were included. Healthy adults were mainly enrolled, with a median age of 44 years. Influenza diagnosis was mainly based on clinical criteria (65.8 % of patients). Oseltamivir was prescribed for 45.4 % of them. In a multivariate analysis, prescription of oseltamivir was associated with the attending physician ($p < 0.001$), positive influenza test ($p < 0.001$) and diabetes ($p = 0.027$). Data on complications were available for 351 patients, and 50 (15.8 %) of them reported at least one. Seven patients required hospitalization. Types of complications (pneumonia, bronchitis, etc.) were not significantly different between patients receiving and those not receiving oseltamivir. In the multivariate analysis, higher oseltamivir prescription rate was associated with fewer complications ($p < 0.001$). Bearing in mind the limitations of a non-randomized study, in a real-life setting, oseltamivir prescription and the rate of complications in patients with influenza were associated with the attending physician, underlying diseases and diagnostic tests. Overall, when the frequency of oseltamivir prescription increased, the influenza-related complications decreased.

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Introduction

Influenza is a common viral infection that usually presents with mild symptoms and subsides without significant complications; however, a significant number of patients seek medical attention [1, 2]. Accordingly, influenza is considered a high-cost infection [2]. Occasionally, complications like pneumonia, bronchitis, otitis or pericarditis occur either due to a secondary bacterial infection or to the natural course of the viral illness [3]. Deaths are primarily attributed to such complications or deterioration of underlying cardiac or lung disease, mainly among the elderly, children and chronically ill patients [4, 5]. Anti-influenza medications have been used for the treatment of patients with severe or complicated influenza, as well as outpatients with milder symptoms at higher risk for development of complications [6, 7]; the profile of such patients is debated [8].

Oseltamivir is the only orally available representative of the neuraminidase inhibitors. Randomized controlled trials and meta-analyses have concluded that the early use of oseltamivir shortens the duration of influenza symptoms by half to one day. Additionally, oseltamivir may reduce influenza-related complications and cost in specific populations [9–11]. However, there are differences in the indications for oseltamivir use in Europe and United States; in

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Europe the manufacturer claims that oseltamivir reduces complications while in the US, it was not allowed to do so due to insufficient evidence on complications [12].

Few data are available regarding influenza in Greece [13–16]. In a previous study, using the SOS network (a network of physicians who perform house-call visits) in Attica, it was shown that physicians prescribed oseltamivir instead of antibiotics when a rapid influenza test was positive [17]. In this study, we sought to evaluate the factors associated with oseltamivir prescription as well as the impact of oseltamivir use on the emergence of influenza complications.

Methods

Study design and patient population

In this prospective observational study, we evaluated patients who called the SOS Doctors in Attica, Greece, during the influenza season between December 2011 and April 2012. A standardized case report form was completed for each patient by the attending physician. Patients with a diagnosis of confirmed or suspected influenza according to the assessment of the attending physician were included in the study. Oseltamivir with or without antibiotics was prescribed at the discretion of the attending physician; in addition, the timing of oseltamivir prescription was not predefined in the protocol of the study. Only patients without complications at the time of the physician's visit were included in the study. Patients with a primary diagnosis of bacterial infection were excluded from the study.

A follow-up phone call was made by the attending physician or the secretariat department of SOS Doctors with the availability of a physician 2 weeks after the medical visit. In the follow-up call, patients were asked if the symptoms subsided or persisted. In the second scenario, patients were asked whether he/she was examined by another physician in the following days, the diagnosis of that visit, and if any other medication was prescribed. Patients with indeterminate outcome (i.e., persistent symptoms without a follow-up visit to a physician or not responding to the follow-up call) were excluded from the analysis regarding complications. The study was approved by the Ethics Committee of the SOS Doctors.

Data collection

Data regarding demographic characteristics (age, gender), patient history (co-morbidity, medications), including the history of a prior episode of influenza in the previous influenza periods, influenza immunization status during the previous 3 years, symptoms and signs, duration of symptoms before physician's visit, and presence of similar symptoms in close contacts were recorded. With regard to influenza, the data collection consisted of the method of diagnosis (clinical or laboratory confirmation), prescription of oseltamivir or other medications, need for hospitalization for any reason, and cure or complications.

Definitions and outcomes

The diagnosis of influenza was either clinical (suspected influenza, based on symptoms and signs of influenza during an epidemic period) or microbiologically assisted (confirmed influenza, using a rapid influenza diagnostic test or polymerase chain reaction [PCR]). The presence of fever or cough and one or more of the following symptoms and signs was used for clinical diagnosis: sore throat, pharyngeal erythema, catarrh/rhinorrhea, nasal congestion, pleuritic chest pain, dyspnea (subjective or confirmed with hypoxemia), frontal or retro-orbital headache, myalgia, arthralgia, weakness or fatigue, red or watery eyes, nausea or vomiting, diarrhea, and tachycardia. The rapid tests used could directly detect influenza A or B viral antigen in throat or nasal swabs.

Cure was defined as remission of all signs and symptoms until the follow-up phone call was made. The emergence of pneumonia, bronchitis, otitis, sinusitis, pericarditis, or other respiratory tract infection during or following the influenza episode was defined as influenza-related complication. High-risk patients for complications were considered those with age over 65 years, chronic cardiovascular disease (other than hypertension), chronic respiratory disease (mainly asthma or chronic obstructive pulmonary disease, [COPD]), diabetes mellitus, hematologic or neurologic disease, obesity, pregnancy, or immunosuppression. Differences in prescription of oseltamivir among the physicians (degree of oseltamivir use) participating in the study was evaluated by comparing physicians prescribing oseltamivir to more than half of their patients (with confirmed or suspected influenza) with physicians that prescribed oseltamivir to less than half of their patients.

Data analysis and statistical methods

Comparison of continuous variables was performed using the Student's *t*-test or Mann-Whitney test (for normally and non-normally distributed variables, respectively). Categorical variables were compared using χ^2. A *p*-value less than 0.05 was defined to indicate statistical significance. Variables that were significantly associated with prescription of oseltamivir or complications were included in multivariate logistic regression models. Diabetes mellitus, obesity, chronic respiratory disease, chronic heart disease,

high-risk patients, use of statins and angiotensin-converting enzyme inhibitors (ACEi), and age were introduced in the multivariate analyses regardless of their association with complications or oseltamivir prescription in the univariate analyses. All analyses were performed with SPSS 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows the characteristics of the 410 patients with confirmed or suspected influenza included in the study. The majority of the patients enrolled were female (63.7 %), the median age was 44 years, and the most commonly encountered co-morbidity was hypertension (17.8 %), followed by endocrine diseases (mainly hypothyroidism, 13.2 %) and obesity (12.7 %). Overall, few patients with chronic respiratory or heart disease were enrolled. The influenza vaccination rate was low; 17.3 % of patients had been vaccinated in any of the previous 3 years, while only 6.6 % had been vaccinated during the current influenza season (2011-2012). The median duration of symptoms prior to the physician's visit and oseltamivir prescription was 48 h (range 2-144). Fever (96.8 %) and cough (91 %) were the most commonly reported symptoms; 43.4 % of patients had a close contact with individuals with similar symptoms. The diagnosis of influenza was based on clinical criteria for the majority of patients (65.8 %). Patients with confirmed or suspected influenza had similar co-morbidity besides cortisol use (higher in confirmed cases) and prior influenza (higher in suspected cases). Regarding symptoms, fewer patients with confirmed influenza had sore throat and nasal congestion, but more had cough and a sense of dyspnea. None of the enrolled patients had an influenza-related complication at the time of the physician's visit.

The prescribed medications for influenza and patient outcomes are presented in Table 2. Oseltamivir was prescribed for 45.4 % of the patients. In addition, antibiotics were prescribed for 17.2 % of those who also received oseltamivir. Antibiotics alone were prescribed for 12.7 % of patients. The rate of antibiotic prescription was not significantly different for patients with suspected and confirmed influenza (22.8 % vs 15.8 %, $p = 0.12$). In the univariate analysis oseltamivir prescription was associated with older age ($p = 0.013$), diabetes ($p = 0.015$), use of statins ($p = 0.034$), a positive direct influenza test or PCR ($p < 0.001$), and the attending physician ($p < 0.001$). On the other hand, oseltamivir was not prescribed when the patient had catarrh ($p = 0.031$), nasal congestion ($p < 0.001$) or headache ($p = 0.013$) or if they had a longer duration of symptoms (>48 h, $p = 0.002$). In the multivariate analysis (Table 3), following adjustment for age and co-morbidity, prescription of oseltamivir was associated with the attending physician ($p < 0.001$), a positive influenza test ($p < 0.001$), and diabetes ($p = 0.027$). Nasal congestion was inversely associated with oseltamivir prescription in the multivariate analysis ($p < 0.001$).

Data on complications were not available for 59 of the 410 patients because these patients could not be contacted by or refused to answer a follow-up phone call. Out of the 351 patients whose outcome could be assessed, 50 (15.8 %) reported a complication, including bronchitis (7.4 %), sinusitis (2.2 %), pneumonia (2 %), pharyngitis (1.1 %), and otitis (0.6 %). Pericarditis, laryngitis, and tonsillitis were reported in one patient each. Seven patients required hospitalization (4 oseltamivir-treated patients). The single death occurred in a 75-year-old female patient with a history of hypertension and hypothyroidism who did not receive oseltamivir on diagnosis.

Types of complications (e.g., bronchitis, pneumonia, etc.) were similarly distributed between patients receiving or not receiving oseltamivir. Complications were inversely associated with the degree of oseltamivir use by the individual attending physician. Among physicians who prescribed oseltamivir to 0 %-50 % of their patients, the rate of complications was 21.7 %; on the other hand, among physicians who prescribed oseltamivir to 50 %-100 % of their patients, the rate of complications was 9.6 % ($p = 0.005$). Other variables associated with more complications in the univariate analysis were influenza vaccination at any time in the previous 3 years ($p = 0.014$), high-risk patients ($p = 0.028$), older age ($p = 0.024$), and use of oseltamivir (0.034). Timing of oseltamivir initiation and vaccination in the current influenza season were not associated with complications. In the multivariate analysis (Table 4), following adjustment for age and co-morbidity, development of complications was associated with prior vaccination at any time ($p = 0.008$) and oseltamivir use ($p < 0.001$). The degree of oseltamivir use by the individual physicians ($p < 0.001$) was associated with fewer complications. If only patients with confirmed influenza were studied, the attending physician and sore throat were associated with lower complications, while prior vaccination was associated with more complications.

Factors associated in multivariate analysis with higher oseltamivir prescription among physicians were a positive test ($p < 0.001$) and use of statins ($p = 0.001$); headache ($p < 0.001$), nasal congestion ($p < 0.001$) and similar symptoms in close contacts ($p = 0.003$) were inversely associated with increased oseltamivir prescription. Factors associated in multivariate analysis with undertaking a diagnostic test were the attending physician ($p < 0.001$), coronary artery disease ($p = 0.028$) and dyspnea on presentation ($p = 0.023$).

Table 1 Characteristics of the 410 patients with influenza or influenza-like illness

Variable	Number of patients, n (%)
Age, years (median, range)	44 (2-96)
Females	261 (63.7)
Males	149 (36.3)
Co-morbidity	
Hypertension	73 (17.8)
Coronary disease	18 (4.4)
COPD/Asthma	17 (4.1)
DM	30 (7.3)
Endocrine	54 (13.2)
Obesity	52 (12.7)
High-risk patients[§]	100 (24.4)
Medications	
ACE inhibitors or ARBs	66 (16.1)
Statins	41 (10)
Prior surgery	64 (15.6)
Prior influenza immunization[*]	72 (17.7)
Before 2009	26 (6.4)
2009	9 (2.2)
2010	9 (2.2)
2011	28 (6.9)
Duration of symptoms before physician's visit, hours (median, range)	48 (2-144)
Symptoms	
Fever	397 (96.8)
Cough	373 (91.0)
Weakness or fatigue	296 (72.2)
Myalgia	292 (71.2)
Nasal congestion	256 (62.4)
Catarrh	244 (59.5)
Sore throat	225 (55)
Headache	215 (52.4)
Similar symptoms in close contacts	178 (43.4)
Method of diagnosis[#]	
Clinical	268 (65.8)
Direct influenza test or PCR[$]	139 (34.2)
Oseltamivir prescription rate per attending physician (median)	34.3 % (IQR 3.8 %-66.7 %)

ACE, angiotensin-converting-enzyme; ARBs, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; DM, diabetes mellitus; IQR, inter-quartile range; PCR, polymerase chain reaction

* Data regarding prior influenza immunization were available for 406 out of 410 patients

Data regarding method of diagnosis were available for 407 out of 410 patients

§ High-risk patients were considered patients with any of the following: chronic cardiac disease (other than hypertension), chronic respiratory disease (e.g., asthma or chronic obstructive pulmonary disease), diabetes mellitus, obesity, or immunosuppression

$ Three patients were tested by PCR; all samples were positive

Discussion

In this prospective cohort of patients with confirmed or suspected influenza during the 2011-2012 influenza season in Athens, Greece, 46 % of patients received oseltamivir. Prescription of oseltamivir was associated with the attending physician, positive influenza test and diabetes. Approximately 15 % of patients developed complications, which mainly included bronchitis, pneumonia and sinusitis. All types of complications were equally distributed

Table 2 Treatment and outcomes of the included patients

Variable	Number of patients, n/N (%)
Oseltamivir	
Oseltamivir only	154/410 (37.6)
Oseltamivir and antibiotics*	32/410 (7.8)
Antibiotics alone	52/410 (12.7)
Remission	300/351 (85.5)
Complications	50/351 (14.2)
Bronchitis	26/351 (7.4)
Sinusitis	8/351 (2.3)
Pneumonia	7/351 (2.0)
Pharyngitis	4/351 (1.1)
Otitis	2/351 (0.6)
Other[¥]	3/351 (0.9)
Required hospitalization	7/409 (1.7)

* Among those who received oseltamivir, 17.8 % also received antibiotics

[¥] "Other complications" comprised laryngitis (n = 1), lymphadenitis (n = 1), and pericarditis (n = 1)

Table 3 Factors associated with oseltamivir prescription in univariate and multivariate analyses

Variable	*p*-value (univariate)	*p*-value (multivariate)	OR, 95 % CI (multivariate)
Older age	0.013	0.61	1.01, 0.99-1.02
Diabetes	0.015	0.027	3.47, 1.16-10.44
Statins	0.034	0.24	1.99, 0.64-6.22
Positive test	<0.001	<0.001	19.72, 9.18-42.34
Attending physician	<0.001	<0.001	0.15, 0.06-0.36
Catarrh	0.031	0.35	0.72, 0.36-1.44
Nasal congestion	<0.001	<0.001	0.39, 0.20-0.77
Headache	0.013	0.81	0.93, 0.51-1.71
Symptoms >48 h	0.002	0.074	0.99, 0.98-1.01

between patients receiving oseltamivir and those not receiving it. Fewer complications were observed when physicians prescribed oseltamivir to the majority of their patients than when physicians prescribed oseltamivir to none or the minority of their patients.

This study showed that physicians have a key role in the management and possibly outcomes of influenza. The prescription of oseltamivir was driven mainly by two factors: the attending physician and a positive influenza test. Physicians ordered an influenza test mainly when patients had co-morbidity (coronary artery disease) or presented with more-severe disease (e.g., sense of dyspnea). Later, they prescribed oseltamivir more commonly to patients with a positive test, and possibly higher co-morbidity (as implied by the use of statins, the presence of diabetes, and vaccination in the previous years).

Table 4 Factors associated with complications in univariate and multivariate analyses

Variable	*p*-value (univariate)	*p*-value (multivariate)	OR, 95 % CI (multivariate)
Oseltamivir to 50-100 %*	0.005	<0.001	0.16, 0.07-0.36
Vaccination at any time	0.014	0.008	3.26, 1.44-7.37
High-risk patients	0.028	0.60	1.34, 0.45-3.99
Age	0.024	0.14	1.02, 0.99-1.04
Oseltamivir	0.034	<0.001	4.90, 2.19-10.97
Diabetes	0.85	0.055	0.21, 0.04-1.03
Obesity	0.07	0.051	2.4, 0.99-5.78

* Oseltamivir prescribed to >50 % of the patients examined by a given physician

Two studies on pediatric populations [18, 19] as well as another one on adults and adolescents [20] reported a lower frequency of influenza-related lower respiratory tract infections and acute otitis media among patients treated with oseltamivir versus placebo. Meta-analyses also showed that influenza-related complications, especially otitis media, were less common in both healthy and high-risk patients with confirmed influenza treated with neuraminidase inhibitors than in those taking placebo [10, 20, 21] or no antiviral therapy [22]. An updated version of the 2003 Cochrane systematic review on the efficacy of oseltamivir to reduce influenza complications in healthy adults concluded that oseltamivir did not reduce complications and called for the manufacturer to release all relevant data [23]. In the meta-analysis performed when these data were disclosed, oseltamivir was associated with reduced investigator-mediated unverified pneumonia in adults, but the difference was not statistically significant when a more detailed diagnostic form for pneumonia was used. Oseltamivir's effect on unverified pneumonia in children and prophylaxis was not significant. There was no significant reduction in risk of unverified bronchitis, otitis media, sinusitis, or any complication classified as serious or leading to study withdrawal [24]. Finally, studies in hospitalized patients with influenza showed that early oseltamivir administration was associated with less-severe disease on presentation and earlier discharge from the hospital [25–27]. On the other hand, when patients with mild influenza were studied, the effectiveness of oseltamivir in reducing complications of influenza was

questionable [28, 29]. In any case, the benefits from oseltamivir use should outweigh the harm in terms of adverse events and resistance, which are rarely studied in depth [12, 22, 30, 31].

The other factor that was independently associated with complications in this study was vaccination in any of the previous 3 years, while vaccination during the current season was not associated with complications. Vaccination reduces the incidence and complications of influenza; however, before 2012 (when the World Health Organization announced that all people above 6 months of age should be vaccinated annually for influenza) the adult candidates for vaccination in Greece were older people (>65 years old) with co-morbidity. Accordingly, risk factors for vaccination in any of the previous 3 years in this study were older age, diabetes, chronic pulmonary diseases, chronic neurologic disorders and influenza in the previous periods (data not shown). In addition, the rate of vaccination in the 2011-2012 influenza period was low. Therefore, vaccination may be a surrogate marker for co-morbidity. Especially, among high-risk patients, vaccination during the previous 3 years was not associated with more complications in this study (data not shown).

In this cohort, the commonly described risk factors for complications after an influenza infection were not identified. Age, obesity, diabetes, pregnancy, and chronic respiratory, cardiovascular, hematologic and neurologic diseases are among these factors. A systematic review concluded that there is lack of strong evidence to support the common belief that the aforementioned risk factors are associated with outcomes after influenza [8]. Among the most important limitations were the lack of power and lack of adjustment for confounders in the studies included in the systematic review. In addition, the level of evidence was described as low or very low.

In this study, treatment was at the discretion of the attending physician. Overall, the rate of antibiotic prescription in this study was not essentially different compared to similar published studies. Unfortunately, inappropriate prescription of antibiotics for respiratory tract infections, even when a viral infection is suspected, is frequent in daily practice [32–34]. This is primarily attributed to difficulties in clinically discriminating bacterial from viral infections [35]. The co-administration of antibiotics with antiviral medications has also been described in the literature, even among ambulatory patients with confirmed influenza [36, 37]. The reasons behind this practice may be efforts to treat or prevent a secondary bacterial infection, the anti-inflammatory effects of antibiotics, efforts to control the seriousness of influenza, presumed antiviral effects, and modification of the host's excessive immune reactions [36]. In addition, the immunomodulatory properties of macrolides have been reported as a potential means to reduce the inflammatory process in influenza and possibly its complications [38]; small trials that refute this notion have been published [39]. Finally, following the A/H1N1 pandemic, several studies have also reported increased demand for antibiotic prescription in the whole or parts of the population, even among patients who under different circumstances would never have done so [40, 41].

The main limitation of the study was the significant percentage of patients lost to follow-up. However, it was expected that it would be difficult to contact all of the enrolled patients by phone. In addition, several patients refused to answer to the follow-up questions. A second limitation might have been the short follow-up period. In addition, we only recorded respiratory tract infections as complications, while complications like deterioration of cardiac and lung function were not recorded, since continuous monitoring would have been required. Third, at follow-up, data regarding compliance with the prescribed medications were not collected. Therefore, the outcomes of the study may be biased by non-adherence of patients, a common event in the treatment of upper respiratory tract infections, even within randomized studies [42–44]. Fourth, the dose of oseltamivir was not pre-specified in the protocol, as in most observational studies, and data regarding dosage were not recorded. However, as in all other countries, in Greece, oseltamivir is prescribed at a dose of 75 mg twice daily for 5 days unless dosage adjustment is required according to renal function. Fifth, due to the small sample size, we were not able to detect differences in hospitalization rates and mortality between patients receiving or not receiving oseltamivir; as expected, few patients required hospitalization. The study did not have the power to show any difference in hospitalization rate and would have required a larger number of patients. Finally, the most appropriate study design to determine whether there could be an improvement in outcomes after oseltamivir prescription would be a randomized control trial, or matched case control studies accounting for co-morbidity, age and disease severity. In this study, oseltamivir prescription was at the discretion of the attending physician, which was proven to be independently associated with lower complications.

In conclusion, this study showed that the rate of complications was lower when physicians prescribed oseltamivir. Distinctive differences in symptoms or risk factors for complications between patients with confirmed or suspected influenza were not observed. However, oseltamivir was prescribed more when the test was positive. In real-life settings, where it is not clear who might really benefit from a medication like oseltamivir, it seems that physicians order a direct influenza test and subsequently prescribe oseltamivir in patients with higher co-morbidity,

who are considered at higher risk for development of complications. Future studies, including randomized trials, should define better the populations for which a test should be performed, identify the patients that would really benefit from oseltamivir prescription, and study the effectiveness and safety of oseltamivir on preventing complications, hospitalizations and possibly deaths in these populations.

Compliance with ethical standards

No funding.

Conflict of interest There is no conflict of interest for all authors.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
This article does not contain any studies with animals performed by any of the authors.

Informed consent Not required.

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