Original Article

Approach to Pandemic 2009 influenza: first report from a main referral hospital for Pandemic H1N1 influenza care in Iran

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Abstract

Introduction: Pandemic H1N1 influenza A (pdmH1N1) was a major health threat worldwide.

Methodology: A prospective cross-sectional study was conducted at Imam Khomeini Hospital in Iran. Cases of suspicious pdmH1N1 patients referred to the emergency ward of the hospital were enrolled in the study, regardless of whether the final location of treatment was the community, the hospital ward, or the intensive care unit. Oseltamivir was administered within three hours of the patient's admission. The median length of stay for hospitalized patients was 3 days.

Results: Gastrointestinal symptoms (nausea [164/434; 37.8%] and vomiting [98/434; 22.6%]) were the most common adverse reactions to oseltamivir in the study population, followed by dizziness (74/434; 17.1%). Out of 434 patients, 209 (48.2%) were treated in the community, 201 (46.3%) were admitted to the general ward in the hospital, and 24 (5.5%) were admitted to an ICU.

Conclusions: This study provided insight on the effectiveness of oseltamivir in treating pandemic influenza A, as well as possible adverse reactions to the drug. The study further drew attention to a variety of pdmH1N1 complications, in particular secondary bacterial pneumonia. We also determined that 2009 influenza A (H1N1) infection-related critical illness and mortality affected fewer elderly than younger patients. Additionally, it was shown that our approach to patients with suspected Influenza A/H1N1 virus in our hospital was compatible with World Health Organization pandemic flu guidelines in our country.

Key words: Oseltamivir; influenza A/H1N1; seasonal influenza

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Introduction

A novel influenza A (H1N1) virus of swine origin was first isolated among people in Mexico during the spring of 2009 [1]. It spread rapidly worldwide, resulting in the first influenza pandemic of this century [2]. In January 2010, confirmed human cases of pandemic influenza A/H1N1 2009 were reported in 195 countries, 22 of which were in the Eastern Mediterranean Region [3]. While most cases of pandemic Influenza A/H1N1 2009 virus infection were self-limited, rigorous complications including fatal outcomes were reported [4-8].

By the time of writing this manuscript, 3,672 cases in Iran were confirmed to have influenza A/H1N1 and 147 patients died [3]. The World Health Organization (WHO) recommends that treatment with oseltamivir be started immediately for patients with symptoms of severe illness, as well as patients who are at higher risk for serious disease from pandemic influenza (*i.e.*, pregnant women, children under age 5 years of age, and those with certain underlying medical conditions) and patients with persistent or rapidly worsening symptoms (*i.e.*, those having difficulty breathing or a high fever lasting beyond three days), no matter when the illness started

and without waiting for laboratory results to confirm infection [9]. When the WHO declared the pdmH1N1 pandemic in April 2009, Iran`s ministry of health attempted to make oseltamivir available for all suspected cases. Brand formulations of oseltamivir, such as Tamiflu (Roche, Basel, Switzerland) and Fluvir (Herero Drugs, Hyderabad, India), in addition to a generic Iranian-manufactured formulation, Flubiovir (Bakhtar-Bioshimi, Kermanshah, Iran), were available before any confirmed cases of pdmH1N1 were identified. Since oseltamivir was not prescribed extensively before the emergence of pdmH1N1 pandemic, a prospective Drug Utilization Review (DUR) was undertaken to evaluate the extent and pattern of oseltamivir use at Imam Hospital, a major referral hospital for infectious diseases in Iran, to assess the impact of remedial strategies implemented.

Methodology

This prospective, cross-sectional study took place from November 2009 through March 2010. The study population consisted of all suspicious cases of pdmH1N1pdmH1N1 presenting at the emergency ward of Imam Khomeini Hospital, regardless of whether the final location of treatment was the community, the hospital ward, or an intensive care unit (ICU).

The data collected included patients' demographic characteristics (age and sex); signs and symptoms upon admission; chief complaints; vital signs; past medical history, including the presence of any comorbidities; history of pdmH1N1 in close relatives; pre-admission antibiotics consumption; history of vaccination against seasonal influenza; the existence of fever and, if present, its duration; laboratory parameters; time elapsed between admission up to the administration of oseltamivir; time elapsed between the appearance of disease symptoms and oseltamivir`s administration; the number of prescribed doses of oseltamivir; length of stay; accompanied treatments; adverse drug reactions of oseltamivir; complications that pdmH1N1 may bring about for patients (if any); medications administered upon discharge; and patients' outcome (discharged with or without complications or death). Pregnancy was documented as well, if applicable. After five days (the completion time of oseltamivir therapy), patients who remained in the community *(i.e.*, those not admitted to hospital) were asked by phone about the adverse reactions of oseltamivir and also about any complications of influenza likely to be caused by H1N1.

The variable "any comorbidity" was defined as referring to heart disease, diabetes mellitus, acquired immune deficiency syndrome (AIDS), respiratory disease, smoking, neurologic disorder, kidney disease, hepatic disease, hematologic disorder, and use of corticosteroids or other immunosuppressant drugs.

The laboratory measurements were compared to normal ranges based on local hospital laboratory reports, and measurements outside the normal range limits were classified as abnormal. Therefore, leukocytosis was defined as a white blood cell (WBC) count greater than 10000/mm^3; leukopenia was defined as a WBC count less than 4000/mm^3; anemia was classified as hemoglobin less than 14 g/dl in males and 12 g/dl in females; thrombocytopenia was determined by a platelet count below 150000/mm3; hyponatremia was defined as a sodium level below 135 meq/l; hypokalemia was identified as a potassium level less than 3.5 meq/l; coagulopathy was characterized by international normalized ratio (INR) above 1.2; and serum creatinine above 1.5 mg/dl was considered as renal failure. Moreover, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) more than two times the upper normal limit (37 IU/1 for males and 31 IU/l for females) and alkaline phosphatase (ALKP) greater than 306 in adults or 1,200 in patients younger than 18 years old were regarded as abnormal liver function tests. In interpreting the vital signs, respiratory rates higher than 25 breaths per minute were regarded as tachypnea, and a pulse rate higher than 100 and less than 60 beats per minutes was defined as tachycardia and bradycardia, respectively.

Statistical Analysis

Descriptive statistics were generated: frequencies (percentages) were obtained for categorical variables and means ± standard deviations (SD) or medians and interquartile ranges (IQRs) for continuous variables.

We assessed overall differences between outpatients and hospitalized individuals in terms of adverse reactions of oseltamivir for categorical variables using the $\chi 2$ test or Fisher's exact test, as appropriate. Moreover, Chi-Square test was used to examine the presence of any relationship between variables of interest and patients' outcome or the incidence of adverse drug reactions in the study

population. We reported results from Chi-square analyses as odds ratios (ORs) and 95% confidence intervals (CIs), with ORs greater than 1.0 signifying greater risk of adverse drug reaction incidence compared with the referent group. *P* values less than 0.05 were considered as significant in this study.

Table 1. Chief complaints, signs and/or symptoms of patients upon admission

Chief Complaint, sign and/or symptom	Frequency/434 (Percent)
Cough	328 (75.6%)
Fever	311 (71.6%)
Myalgia	308 (70.1%)
Shaking Chills	295 (67.9%)
Headache	269 (62.1%)
Dyspnea	235 (54.2%)
Nausea	234 (53.9%)
Malaise	228 (52.4%)
Sore throat	159 (46.3%)
Arthritis	177 (40.8%)
Vertigo	174 (40%)
Chest pain	159 (36.6%)
Vomiting	152 (35%)
Rinorrhea	129 (29.7%)
Diarrhea	120 (27.6%)
Ear pain	58 (15.3%)
Palpitation	62 (14.2%)
Stomach pain	58 (13.4%)
Cyanosis	39 (8.9%)
Loss of conscious	35 (8.2%)
Cold sore	8 (1.8%)

Results

All suspected cases (n = 434) for infection with the Influenza A/H1N1 2009 virus from November 2009 through March 2010, were included in this study. The results of real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) showed that from the patients enrolled, 150 were confirmed positive for influenza A/H1N1. The mean age of infected individuals included in this analysis was 34.7 ± 16.1 years (range: from < 1 to 86 years old). Males accounted for 215 (49.5%) of the infected cases and females comprised 219 (50.5%) individuals, among whom 30 (13.7%) were pregnant. The most frequent clinical pictures and chief complaints of patients were cough 328 (75.6%), fever 311 (71.6%), myalgia 308 (70.1%), shaking chills 295 (67.9%), headache 269 (62.1%), dyspnea 235 (54.2%), and gastrointestinal symptoms including nausea 234 (53.9%), vomiting 152 (35%) and diarrhoea 120 (27.6%). We also had 35 (8.1%) patients who presented with loss of consciousness. The frequencies of all the chief complaints are summarized in Table 1. There were 187 (43.1%) patients who complained of more than one of the above-mentioned symptoms.

Table 2. The comorbidities of hospitalized patients included in the study

Comorbidities	Frequency/225 (Percent)
Respiratory	118 (52.4%)
Drug History of Corticosteroids	73 (32.4%)
Cardiovascular	73 (32.4%)
Smoking	51 (22.7%)
Neurologic	33 (14.7%)
Hematologic	24 (10.7%)
Diabetes Mellitus	22 (9.8%)
Renal	16 (7.12%)
Hepatic	11 (4.9%)
AIDS[1]	10 (4.4%)
Transplantation	2 (0.9%)

1 - Acquired immune deficiency syndrome

There were 136/434 (31.3%) patients who had a history of influenza A/H1N1 in a family member. The proportion of patients who were not vaccinated against seasonal influenza was 379/434 (87.3%). From the enrolled individuals, 67/434 (15.4%) patients who went to the hospital after a long duration of illness had taken antibiotics by self-prescription.

The location of care for the patients was determined as follows: 209/434 (48.2%) patients remained in the community; 201/434 (46.3%) were admitted to the general ward in the hospital; and 24/434 (5.5%) were admitted to an ICU. Other vital signs of hospitalized patients were as follows:

tachycardia was seen in 49 (21.8%); bradycardia in 2 (0.8%); tachypnea in 107 (47.6%); and 20 (9.1%) were hypotensive. Of the 225 patients admitted to the ward or ICU, 173 had comorbidities. Respiratory (118/225; 52.4%) and cardiovascular (73/225; 32.4%) diseases were the most frequent underlying conditions (Table 2).

The following laboratory parameters were recorded for hospitalized patients (n = 225) at the time of admission: leukocytosis in 66/225 (29.3%); leukopenia in 19/225 (8.4%); anemia in 85/225 (37.8%); thrombocytopenia in 35/225 (15.5%); electrolyte imbalances (hyponatremia) in 40/225 (17.8%); hypokalemia in 15/225 (6.7%); coagulopathy in 35/225 (15.6%); serum creatinine above 1.5 mg/dl in 10/225 (4.4%) of patients. Elevated liver enzymes AST was seen in 36/225 (16%) patients; elevated ALT in 28/225 (12.4%); and elevated ALKP in 7/225 (3.1%). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as markers of inflammation, rose in 34/225 (15.1%) and 27/225 (12%) patients, respectively.

Table 3. Adverse reactions of oseltamivir

Adverse Drug Reaction	Frequency(Percent)
Nausea	164(37.8%)
Vomiting	98(22.6%)
Dizziness	85(19.6%)
Gastric pain	64(14.7%)
Nightmare	59(13.6%)
Hallucination	24(5.5%)
Diarrhea	2(0.5%)
Itching	2(0.5%)
Seizure	1(0.3%)
Flushing	1(0.3%)
Headache	1(0.3%)
Impaired LFT[1]	1(0.3%)

1. Liver Function Test

Clinical outcome

The median interval before initiation of treatment was four days (IQR 2-7). Oseltamivir was administered within three hours of admission time (IQR 4-7) for infected individuals. The length of stay for hospitalized patients had a median of three days (IQR 2-6). The majority of patients 327/434 (75.3%) had received 10 tablets or capsules of oseltamivir for treatment. Accompanied prescribed medications for hospitalized patients were ceftriaxone for all patients, azithromycin for 194/225 (86.2%), patients and vancomycin in 156/225 (69.3%) patients. A few patients also received other antibiotics during their hospitalization, such as co-amoxiclav in 14/225 (6.2%); imipenem in 14/225 (6.2%); tazocin in 3/225 (1.3%); clindamycin in 3/225 (1.3%); metronidazole in 2/225 (0.9%); meropenem in 1/225 (0.4%); teicoplanin in 1/225 (0.4%); and cotrimoxazole in 1/225 (0.4%).

The most common adverse drug reactions to oseltamivir in the study population (n = 434) are shown in Table 3: symptoms of nausea in 164/434 (37.8%); vomiting in 98/434 (22.6%); and dizziness in 85/434 (19.6%). Complications of pdmH1N1 were recorded in all hospitalized patients (n = 225); respiratory complications (157/225; 69.8%) and central nervous system disorders (34/225; 15.1%) were the most common, followed by gastrointestinal, cardiovascular, renal, and hepatic complications .

The amount of prescribed oseltamivir was the strongest univariable correlate with oseltamivir's adverse reaction incidence (OR = 3.843, 95% CI 1.093-13.509, p = 0.04) in hospitalized patients followed by duration of hospitalization more than five days (OR=3.066, 95% CI 1.151-8.162, p = 0.015). The presence of a drug history of corticosteroids significantly increased the odds of stomach pain in infected patients (OR = 2.433, 95% CI 1.187-4.988, p = 0.034). The odds ratio of hallucination as an adverse drug reaction among patients with loss of consciousness on admission time was 8.222 (95% CI 1.731-39.062, p = 0.039). Upon discharge, co-amoxiclav was prescribed for 74/225 (32.9%) of hospitalized patients, cefixime and azithromycin were each prescribed for 4/225 (1.8%) patients, and the remaining patients did not receive any medications.

The outcome of patients based on their location of care was recorded. Of those who remained in the community, 124/209 (59.3%) recovered without any complications, while one or more complications of pdmH1N1 arose in 84/209(40.2%) patients. From hospitalized patients in the general wards, 75/201 (37.3%) were discharged without any complications; 105/201 (52.2%) were discharged with at least one complication of H1N1; and there were 9/201 (4.5%) fatal cases. The remaining cases of patients in this location were not followed up. Twenty-four of the most critical cases were admitted to the ICU. Of

these, 20/24 (83.3%) patients, who were predominantly younger cases, died; 3/24(12.5%) patient were discharged with complications; and only 1/24 (4.2%) case was discharged without any complications.

Discussion

We describe a cohort study of 434 patients identified in Iran who were hospitalized for 2009 pandemic influenza A (H1N1) virus infection between November 2009 and March 2010. The decision to admit patients to the hospital was performed according to the clinical condition of patients. Since Imam Hospital was introduced as the referral hospital for influenza in the peak time of pdmH1N1 infection in Iran, physicians' measures had focused on managing clusters of infections and complications of the illness instead of hospitalization. This policy was the same as that of China`s public health strategy [10]. None of our patients were vaccinated against pandemic influenza due to unavailability of the vaccine in Iran at the time of study. Furthermore, none of our patients had received pre-admission oseltamivir since this medication is available only in specific hospitals selected for the management of influenza A/H1N1 infected patients.

When compared with similar studies performed in the United States [11], Japan [12], Mexico and other countries [13], fewer patients in our cohort (71.6%, vs. above 90% in other studies) presented with fever, and the most frequent chief complaint of patients in our study was cough. This phenomenon may be in part due to the self-prescription of acetaminophen in case of fever in patients. In contrast, the incidence of gastrointestinal disorders (nausea, vomiting and diarrhea) was higher than previously reported [10]. In our study, 29.3% of hospitalized patients had leukocytosis and 8.4% patients had leucopenia similar, to the report of hospitalized patients in California [14].

In an updated 2006 Cochrane review on neuraminidase inhibitors [15], the most commonly reported adverse reactions in the trials were vomiting [16] and nausea in adults, but no behavioral disturbances or deaths [15]. The lowest incidence of these adverse reactions in patients treated with oseltamivir was 4.7-8.4% [17, 18]. In our study, these adverse reactions were higher and estimated as nausea in 37.8% and vomiting in 22.6% of patients. Although the hospitalized patients with pneumonia received azithromycin, which could induce gastrointestinal symptoms, the majority of our patients were treated in the community with only oseltamivir. Therefore, we could ascribe this adverse effect to oseltamivir. Previous studies reported a confused mental state and hallucinations to be as prevalent as 9.4% and 6.4%, respectively [17,18]; however, dizziness, the most frequent neuropsychiatric adverse reaction of oseltamivir, took place in 19.5% of our patients, while the incidence rate of hallucination in our study was 5.5%. We had a single case of seizures, rash, and impaired liver function test (LFT) due to ingestion of oseltamivir, and these adverse reactions were reported in other studies as well [10,18,19].

Our study further demonstrated an association between the length of oseltamivir's prescription and the incidence of its adverse reactions among hospitalized individuals. In circumstances where oseltamivir was used beyond five days or exceeded its routine dosage in pdmH1N1 (75 mg BD), a greater number of patients suffered from oseltamivir`s adverse drug reaction. Similarly, in a recent systematic review, extended-duration and higher doses of oseltamivir were associated with increased nausea and vomiting as the most common ADRs in immunocompetent healthy subjects when oseltamivir was taken for chemoprophylaxis [20]. Another finding of our study was a strong association between drug history of corticosteroids and the incidence of stomachache as oseltamivir`s ADR. In view of the fact that glucocorticoids were found to be associated with a significant increase in the risk of gastrointestinal tract adverse events (RR = 2.91, 95% CI 1.25 to 6.77, p = 0.02) [21], this result could be explained by the synergic effect that corticosteroids may have in inducing stomachache with oseltamivir. According to the results of our study, patients with loss of consciousness at their presentation had suffered from hallucination to a greater extent than the others. Hallucinations can be the result of several processes, including disturbances of brain anatomy, brain chemistry, previous experiences, and psychodynamic mechanisms defined as the emergence of unconsciousness into consciousness [22, 23]. Hence, unconsciousness upon presentation could increase the incidence of hallucination as oseltamivir`s ADR.

In accordance with WHO guidelines, patients suffering from influenza A/ H1N1 who are at risk for pneumonia should be treated with oseltamivir once symptoms develop, if feasible [24]. Moreover, it is implicit that oseltamivir can reduce the number of pdmH1N1 complications that contribute to the

hospitalization and mortality associated with the disease [25]. The median interval for the initiation of oseltamivir in our patients was four days after the appearance of symptoms. This delay in treatment was due to the fact that patients did not immediately go to the hospital because they thought that their symptoms were owing to a common cold or seasonal influenza and would resolve on their own. It is noteworthy to mention that upon admission, oseltamivir was administered within three hours. Since the importance of promptly treating r pregnant patients is widely recogonized [26], oseltamivir was started without delay and no mortalities occurred in this group of patients.

Secondary bacterial pneumonia occurs with influenza A/H1N1 and presents a challenge for clinicians to make decisions about antibiotic treatment of influenza patients with suspicious lower respiratory tract disease. The clinical approach of many physicians to influenza A/H1N1 pneumonia has been to prescribe antibiotics empirically for potential community-acquired pneumonia, regardless of the clinical presentation or chest radiography findings, founded on the concept that during past influenza pandemics a large number of mortalities were a result of bacterial pneumonia [27]. It is recommended that empirical initial therapy with broad-spectrum antibiotics against methicillin-resistant *Staphylococcus aureus* (MRSA), in addition to *Streptococcus pneumoniae* and other common respiratory pathogens be prescribed for pdmH1N1 patients [28]. However, there is a report by Dr. Ellis on swine influenza where antibiotics were not prescribed empirically [29]. We prescribed antibiotics in our patients as soon as the first symptoms indicating pneumonia, particularly respiratory distress, developed.

Our data showed that mortality in the current outbreak of influenza A/H1N1 in Iran was concentrated in relatively healthy adults (mean ± SD; 42.2 ± 15.5). The ICU was the location of care for only three patients older than 65 years in this study. This is inconsistent with the demonstrated results of a study performed in Canada on critically ill patients [5]. Furthermore, we could not find any correlations between older age and the incidence of mortality. This could be explained by the fact that patients in this age group may have a cross-reactive antibody to 2009 influenza A (H1N1) to a greater extent than younger patients [30].

Limitations

Our study was not without limitations. We could not obtain the data on all patients infected with H1N1 in Iran, and could evaluate only the patients referred to Imam Khomeini Hospital, the main referral hospital. Secondly, follow-up for the patients treated primarily in the community was performed by phone call; therefore, the complications and adverse events were evaluated based on the patient's self-judgments and not clinical evaluation by physicians.

In conclusion, close observation of patients infected with the 2009 pandemic influenza A (H1N1) virus provided us with insight on the effectiveness of oseltamivir in treating influenza, as well as the possible adverse reactions to the drug. The study also revealed a variety of pdmH1N1 complications, in particular secondary bacterial pneumonia that may develop in infected patients. Furthermore, we have confirmed that critical illness and mortality affect fewer elderly patients than younger patients with 2009 influenza A (H1N1) infection-related affects.

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