Post-Exposure Prophylaxis for H1N1 with Oseltamivir in Renal Allograft Recipient -Safe and Effective without any Immunosuppressive Drug Interaction

Vivek Kute¹, KR Gopiani¹, SM Godara¹, PR Shah¹, AV Vanikar ², HL Trivedi¹

Abstract

Kidney transplant recipients are at a high risk for H1N1 infection associated complications during the current pandemic. Prevention of infection by immunization, together with early recognition and prompt antiviral treatment are critical. Post-exposure prophylaxis of H1N1 with oseltamivir was safe, effective and well tolerated to prevent H1N1 influenza A virus infection in newly transplanted renal allograft recipient receiving triple immunosuppression without any interaction with tacrolimus level. Oseltamivir was effective for post-exposure prophylaxis of H1N1 in close contact.

Introduction

According to the World Health Organization (WHO), 94,500 laboratory-confirmed cases of human swine flu (H1N1) have been reported in 100 countries.¹ WHO declared pandemic of H1N1 on June 11, 2009. Individuals at risk for complications include those younger than 2 or over 65 years; pregnant; or with a weakened immune system such as solid organ transplant recipients.² As of January 1, 2010, samples from 112766 persons have been tested for influenza A H1N1 swine flu in government laboratories and few private laboratories across India of which 23.09% (26039) were positive (Ministry of Health and Family Welfare, Government of India-issued by Press Information Bureau of India).

H1N1 Patient

A 46 years male resident of Gujarat was admitted for fever, cough with expectoration, and breathlessness for 15 days. His past medical history included end-stage renal disease (ESRD) from hypertension. Prior to hospitalization he was treated in private hospital with intravenous antibiotics and anti-fungal for 7 days, however his clinical condition deteriorated. On admission, his temperature was 38°C; respiratory rate was 30/min, and arterial oxygen saturation on room air was 86 %. His hemoglobin was 7.8 gram%, WBC count 2.6 x 10⁸ /cmm and platelet count 4 x 10⁹ /cmm. His S. creatinine (SCr) was 6 mg %. His S. creatinine (SCr) was 6 mg %. X-ray chest showed bilateral pneumonia. Subsequently he required invasive ventilation. Real-time reverse-transcriptase–polymerase-chain-reaction assay (RT-PCR) from nasal and pharyngeal swab showed H1N1. Positive contact history matched with RT-PCR confirmed diagnosis of H1N1 during prior hospitalization. Oral oseltamivir with a renally adjusted dosage was begun. He was shifted to isolation ward. Patient died on day 5 of admission. Post-exposure chemoprophylaxis with oseltamivir was given to close contact.

Renal Transplant Recipient

A 40 year female resident of Gujarat with history of chronic glomerulonephritis-ESRD on hemodialysis for 4 months was admitted for renal transplant with husband as donor. She had past history of pulmonary tuberculosis and hypertension. She had 2 children and received 2 units of red cells for anemia. Due to pre-sensitization she was subjected to desensitization protocol of bortezomib (1.3mg/m² × 6 doses), six therapeutic plasmapheresis (35ml/kg), intravenous immunoglobulin (5 grams × six doses) and mycophenolate mofetil (MMF) (1.5gram daily x 4 weeks) She received intra-operative induction therapy with methylprednisolone, 500 mg and anti-thymocyte globulin (ATG) (1.5 mg/kg).She had immediate good allograft function with 14 liter urine output and her S. Cr was 0.9mg%. For maintenance immunosuppression, she received prednisolone (20 mg daily), tacrolimus (0.08 mg/kg/day) and MMF (1.5 gram daily x 4 weeks). She received intra-operative induction therapy with methylprednisolone, 500 mg and anti-thymocyte globulin (ATG) (1.5 mg/kg). She had immediate good allograft function with 14 liter urine output and her S. Cr was 0.9mg%. For maintenance immunosuppression, she received prednisolone (20 mg daily), tacrolimus (0.08 mg/kg/day) and MMF (1.5gram/day). Her immediate post- transplant period was complicated by close contact with patient of pneumonia for 3 days which later was diagnosed to have RT-PCR proven H1N1. She had no history of H1N1 vaccination in pretransplant period. In view of significant exposure to H1N1 infection and her immunosuppression including desensitization protocol, oseltamivir prophylaxis (75 mg once daily) was administered for 10 days. H1N1 vaccine was not available to our patient. Immunosuppressive therapy was not reduced. The trough tacrolimus level before and after oseltamivir prophylaxis, were 11.3 and 11.1 ng/ml (reference range: 4-20 ng/ml).The remainder of her posttransplant course was uneventful; she was discharged on 12th posttransplant day with no signs/symptoms of H1N1 and with continued excellent graft function (SCr 0.8 mg %). Throughout her course, she did not manifest any signs/symptoms of influenza like illness/ fever/ cough/ sore throat/ headache / running nose. She did not develop any adverse effects from oseltamivir prophylaxis including any drug interaction with immunosuppressive therapy.

Discussion

While solid organ transplant recipients under immunosuppressive therapy may be at higher risk for H1N1 complications when exposed to close contacts, our report suggested a benefit...
Table 1: Therapeutic Characteristics of Antivirals for Human Swine Flu H1N1

<table>
<thead>
<tr>
<th>Route</th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability (%)</td>
<td>Oral</td>
<td>Inhaled</td>
</tr>
<tr>
<td>Half-life(hours)</td>
<td>75 once daily</td>
<td>10 twice daily</td>
</tr>
<tr>
<td>Dose (prophylaxis) mg/day</td>
<td>75</td>
<td>10</td>
</tr>
<tr>
<td>Dose(treatment)mg/day</td>
<td>150</td>
<td>20</td>
</tr>
<tr>
<td>Renal dose adjustment GFR</td>
<td>&lt;30</td>
<td>None</td>
</tr>
<tr>
<td>Side effects</td>
<td>Nausea, Abdominal discomfort</td>
<td>Wheezing, Bronchospasm</td>
</tr>
<tr>
<td>Dose (treatment) mg/day</td>
<td>GFR &gt;30: 75 twice daily</td>
<td>10 twice daily</td>
</tr>
<tr>
<td></td>
<td>GFR 15-30: 75 once daily</td>
<td>10 twice daily</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis: 30 after alternate dialysis</td>
<td>10 twice daily</td>
</tr>
<tr>
<td></td>
<td>Peritoneal dialysis: 30 once a week</td>
<td>10 twice daily</td>
</tr>
<tr>
<td></td>
<td>Kidney transplant: According to GFR</td>
<td>10 twice daily</td>
</tr>
</tbody>
</table>

CLcr - Creatinine clearance; GFR - Glomerular filtration rate

**Oseltamivir prophylaxis**: Neither did our patient develop manifestations of flu-like illness nor adverse effects from 10 day course of oseltamivir.

Where the risk of human-to-human transmission of influenza is high/low and likelihood of complication of infection is high, (due to strain/baseline risk of exposed group) oseltamivir/zanamivir might be used as post-exposure chemoprophylaxis for individuals at risk' groups. (Weak recommendation, moderate quality evidence). Chemoprophylaxis should begin as soon as exposure identified and continued for 5-7 days after last known exposure.3

In kidney transplant patients, oseltamivir has no interactions with cyclosporine; tacrolimus, MMF and steroids, and it can be safely used. The drug is usually well tolerated; however, side effects like dizziness and gastrointestinal disorder may be seen at higher doses. A thorough knowledge of dosing schedule of oseltamivir and zanamivir is a must to avoid undesirable side effects.4

H1N1 vaccine is not available to our patient. Because of desensitization protocol and ATG induction together with maintenance triple immunosuppression, we gave 10 days post exposure chemoprophylaxis with oseltamivir to our patient.

Lymphocyte depletion as well as enhanced immune suppression, particularly high doses of steroids, are likely to prolong viral replication. Prophylaxis may be considered for recent transplant recipients/ recipients of lymphocyte depleting antibodies, and those in whom immunization is contraindicated.3 Immunization with an inactivated vaccine is recommended for transplant patients, should receive at least one dose of H1N1 vaccine. If a transplant recipient has already received vaccine pre-transplant, there is no need to give a repeat dose post-transplant.5

Given the rapid spread of virus, transplant recipients can begin to receive H1N1 vaccine as soon as one month post-transplant. However, the immune response of early vaccination may only be partially protective.

Recipients should be monitored closely for allograft rejection, and for co-infection or super-infection.6 In addition, clinicians should consider minimizing immunosuppression if possible although the risk of rejection in the early transplant period must be weighed against the risk of influenza on an individual basis.6

The excretion of oseltamivir carboxylate is primarily via the kidneys. A 30 mg dose of oseltamivir given once weekly in CAPD or after alternate sessions in HD patients provides sufficient exposure to oseltamivir carboxylate to allow safe and effective anti-influenza treatment and prophylaxis.7

Oseltamivir should be started empirically based on clinical judgment as early as possible even before definitive diagnostic test results become available, i.e., treatment should not wait for laboratory confirmation of influenza. Treatment is most effective when started in the first 48 hours of illness. However, evidence suggests treatment may benefit patients with prolonged or severe illness even when started more than 48 hours after the onset of illness.8

The growing incidence of H1N1 virus infection and second-generation cases suggested that the H1N1 virus was being spread via human-to-human transmission. To prevent the transmission in health care settings, US CDC provided interim recommendations to protect medical workers from being infected, including personal protective equipments and management. All the accompanying families, close health care workers and high risk patient were put on oseltamivir chemoprophylaxis (75 mg daily for 10 days). When infection-control measures were strictly enforced- with patients confined and isolated in hospital area and N95 respirators used in addition to goggles, gowns, and gloves, as well as liberal use of gel-alcohol hand sanitizer and surgical masks to prevent infection - no health care workers had influenza-like illness. These measures proved to be effective, and no cases of influenza-like symptoms occurred in close family members and health care workers.9

**Conclusions**

Post-exposure prophylaxis of H1N1 with oseltamivir was safe, effective and well tolerated to prevent H1N1 influenza A virus infection in newly transplanted renal allograft recipient receiving triple immunosuppression without any interaction with tacrolimus level. Oseltamivir was effective for post-exposure prophylaxis of H1N1 in close contact.7

**References**

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Cardiac Conduction System Affection in a Case of Swine Flu

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Abstract

We present a case of swine flu presenting as bilateral pneumonia with involvement of cardiac conduction system in the form of increased PR interval and sinus bradycardia during the initial course of disease process. To the best of our knowledge, affection of conducting system in a case of swine flu has not been reported in the literature so far.

Introduction

Cardiac conduction system involving SA node and AV node has been found to be affected by various systemic disorders including infections (Viral myocarditis, endocarditis, Lyme disease, Chagas disease, Diphtheria, tuberculosis, syphilis, rheumatic fever etc.), infiltrative (Amyloidosis, haemochromatosis, sarcoidosis), collagen vascular disorders, drug toxicity and post cardiac surgery.

Affection of conducting system and myocarditis by various viral disorders in not a rare entity. This has been reported in coxsackie virus, EBV virus, adenovirus, hepatitis C, HIV etc. Influenza A infection is a debilitating respiratory illness rarely affecting the Cardiovascular system.

Influenza A and B viruses are enveloped viruses with a segmented genome made up of eight single-standard RNA segments of 890 to 2341 nucleotides each.1 Influenza A is further subdivided into 16 hemagglutinin (H1 to H16) and nine neuraminidase (N1 to N9) subtypes on the basis of the antigenicity of the surface proteins hemagglutinin and neuraminidase. Cardiac involvement has been reported in cases of swine flu. Influenza A and B viruses are enveloped viruses with a segmented genome made up of eight single-standard RNA segments of 890 to 2341 nucleotides each. To the best of our knowledge, affection of conducting system in a case of swine flu has not been reported in the literature so far.

Epidemiological studies have demonstrated an association between influenza epidemics and cardiovascular mortality.

Case Report

A patient, 42 years old male, presented in the department of cardiology as a case of accelerated hypertension with shortness of breath and low grade fever for three days. Patient had past history of hypertension with no documents available. There was no history of tuberculosis, diabetes or any other significant illness. At the time of admission, patient was conscious, oriented. His vital signs revealed pulse = 102/min regular, blood pressure = 220/120 mmHg, respiratory rate = 34/min with mild cyanosis. Jugular venous pressure was normal. Respiratory system examination revealed bilateral coarse crepts and rhonchi. Other system was normal except the presence of soft left ventricular third heart sound on cardiac auscultation. On investigations, sputum was positive for H1N1 virus. At the time of admission, Hb=12.3g%, TLC=4300 cells/mm3, polymorphs were 83%, ESR=50mm of 1st Hour, Blood sugar = 61.0 mg/dl, blood urea=182.0 mg/dl, S.creatinine=1.6mg/dl, CPK-MB=27.7 IU/L, S.Sodium = 138.8 meq/dl, S.Potassium=5.1 meq/dl, S.calcium=8.9 meq/dl, S.P02=94%, LFT was normal, pH=7.14 with respiratory and metabolic acidosis in arterial blood gas analysis. Chest Skiagram showed bilateral heterogenous infiltration in lower zones with cardiothoracic ratio of 0.6. Echocardiography showed left ventricle hypertrophy with no other abnormality. Initially patient was treated as a case of left ventricular failure but patient did not respond to decongestive therapy and had persistent low arterial oxygen saturation. On the basis of disproportionate and persistent signs and symptoms, diagnosis of bilateral bronchopneumonia had been considered. Patient was taken on mechanical ventilation due to low oxygen saturation and deteriorating clinical status. On third day of admission, repeat investigations showed Na+ S.Sodium =145.0 meq/l, S.Potassium =4.9 meq/l, S.P02= 94%, pH=7.30, blood urea=15.0 mg/dl, S. creatinine= 1.0 mg/dl, CPK-MB=3.0. Electrolytes were within normal limits during the further course of the disease. Electrocardiogram (Fig.1a) on day 1 showed HR=88/min, regular, normal axis, LVH, T in lead I and aVL on day 3rd electrocardiograph (Fig.1b) showed HR=90/min, regular and PR interval=0.28 sec. on day 4th electrocardiograph (Fig.1c) showed severe sinus bradycardia with heart rate of 36/min, PR interval was 0.28 sec, QTC=49 sec, and QRS duration was 0.12 sec. Thus, patient had involvement of cardiac conduction tissue involvement on the 3rd, 4th and subsequent days of disease course. Patient died on 9th day.

Discussion

We have reported a case of swine flu presenting as bilateral lobar pneumonia with involvement of cardiac conduction system. In our case, PR interval was normal during first three days of onset of symptoms. On 4th day, we found an increase in PR interval (0.28 s) with deterioration in patient’s clinical status with refractory hypotension not responding to vasopressors. On 7th day, patient developed sinus bradycardia with heart rate of 36/min, PR interval of 0.28 sec. Initially patient had hypoxia, increased blood urea, normal electrolytes and respiratory and metabolic acidosis, which improved with treatment. The temporal sequence of increase in PR interval and sinus bradycardia after 3- days of onset of symptoms is suggestive of progressive increase in involvement of conducting tissue and...