Intravenous zanamivir in critically ill patients due to pandemic 2009 (H1N1) influenza A virus

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ABSTRACT

Introduction: The 2009 (H1N1) influenza A pandemic started in April 2009 and has since spread globally. We have noticed that critically ill patients with confirmed pandemic 2009 (H1N1) influenza A require mechanical ventilation. This paper describes the use of intravenous zanamivir in this group of patients.

Methods: Patients who had severe pneumonia with 2009 (H1N1) influenza A and required intravenous zanamivir were referred to the Infectious Diseases Department of our institution. Clinical data was collected from these patients. Clinical samples were sent to the National Public Health Laboratory for sequencing.

Results: A total of five patients used intravenous zanamivir from April 8 to May 8, 2010. Only one death was reported. There were no side effects attributable to the use of intravenous zanamivir. H275 mutation, which confers resistance to oseltamivir, was seen in a subpopulation of the virus in one case.

Conclusion: Physicians can consider using intravenous zanamivir for the treatment of critically ill patients with 2009 (H1N1) influenza A infection.

Keywords: H1N1 virus, influenza, intensive care unit, pneumonia, zanamivir

Singapore Med J 2011;52(7):481-485

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INTRODUCTION

Almost every country has reported cases of the pandemic 2009 (H1N1) influenza A (henceforth denoted as 2009 H1N1) since the first case was reported in April 2009 in Mexico. The illness has been largely self-limiting and the reported mortality has varied.[1,2] The case fatality rate is estimated to be less than 0.5%.[1-3] However, patients with 2009 H1N1 have suffered severe pneumonia, with development of acute respiratory distress syndrome (ARDS).[4,5]

Treatment with neuraminidase (NA) inhibitors, oral oseltamivir or inhaled zanamivir is recommended for patients with severe illness, children below two years of age, adults aged ≥ 65 years, pregnant women and those with multiple comorbidities.[6] Early treatment may reduce complications, including the need for mechanical ventilation, and mortality.[6,7] However, treatment of ventilated patients suffering from influenza (including 2009 H1N1) infection is more complex. This is because critically ill patients with ARDS may not absorb drugs well,[8] and the use of aerosolised zanamivir through the ventilatory circuit is not recommended,[9] as it will precipitate and obstruct the ventilatory tubing. We report the use of intravenous (IV) zanamivir in patients with 2009 H1N1 infection and severe pneumonia.

METHODS

Patients with severe pneumonia caused by 2009 H1N1 who required mechanical ventilation were managed at our hospital's Medical Intensive Care Unit (MICU). All the cases were confirmed to have pandemic 2009 (H1N1) influenza A using polymerase chain reaction (PCR). Those who required IV zanamivir were referred to the Department of Infectious Diseases. Each case was assessed for suitability for IV zanamivir based on the severity of infection, the lack of response to oral oseltamivir and lack of gastrointestinal absorption. The clinical data of patients using IV zanamivir was collected. The local Health Sciences Authority and the hospital's Pharmacy and Therapeutics Committee approved the use of IV zanamivir (provided on a compassionate-use basis by GlaxoSmithKline, Singapore). Written consent was obtained from the patients' next-of-kin or surrogate decision makers. IV zanamivir was used in accordance with the guidelines contained within the Guidance Document issued by the manufacturers.[10]

Clinical samples (either endotracheal tube aspirates or throat swabs) were sent to the National Public Health Laboratory (NPHL), Singapore, for sequencing of the haemagglutinin and NA genes.[11] Nucleic acid extracted

Table I. Demographics, treatment and outcome of critically ill patients treated with IV zanamivir in the intensive care unit.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (yrs)	44	36	47	42	66
Gender	Male	Male	Female	Male	Male
BMI (kg/m^2)	25.1	27.9	35.1	26.3	21.4
Race	Chinese	Chinese	Indian	Bangladeshi	Chinese
Medical history	TIA, childhood asthma	Nil	HPT, newly diagnosed DM	Nil	IHD, SLE
Duration of symptoms on presentation (days)	7	5	2	14	8
Duration of oseltamivir prior to IV zanamivir (days)	3	3	2	4	0
PaO_2/FiO_2 ratio*	60	83	64	53	207
APACHE II	10	11	15	8	13
Duration of IV zanamivir (days)	6	5	5	5	5
Ventilator days	9	11	15	15	4
Procalcitonin median; range (UG/L)	1.18; 0.67–2.0	0.79; 0.79–0.84	0.13; 0.13–4.1	1.35; 0.92–2.3	30.7; 0.77–73.9
Concurrent Antibiotics†	Ceftazidime, moxifloxacin, vancomycin	Ceftazidime, azithromycin, cloxacillin, caspofungin	Ceftazidime, Azithromycin, cloxacillin	Meropenem, levofloxacin	Meropenem, levofloxacin
Concurrent infection	-	Candidaemia *(Candida grabrata)*	VAP – no organisms grown	VAP – MDR *Acinetobacter baumannii*	-
Complication during ICU	Acute kidney injury thrombocytopenia	Acute kidney injury, haemorrhagic pericardial effusion	Myocarditis	Pulmonary haemorrhage, acute kidney injury	Pulmonary haemorrhage, acute kidney injury
Use of ECMO	Yes	Yes	Yes	Yes	No
Outcome	Dead	Alive	Alive	Alive	Alive

* Ratio of arterial oxygen pressure to the fractional concentration of inspired oxygen; measured on admission to intensive care unit.
† Antibiotics that were given concurrently with IV zanamivir only.
BMI: body mass index; TIA: transient ischaemic attack; HPT: hypertension; DM: diabetes mellitus; IHD: ischaemic heart disease; SLE: systemic lupus erythematosus; VAP: ventilator-associated pneumonia; MDR: multidrug resistant; ICU: intensive care unit, ECMO: extracorporeal membrane oxygenation; APACHE: Acute Physiology and Chronic Health Evaluation; IV: intravenous

from the clinical samples was used as the sequencing and pyrosequencing template for each case. Pyrosequencing of NA-H275 was also performed for antiviral susceptibility testing, according to the United States Centers for Diseases Control and Prevention protocol published by the World Health Organization on PyroMark™ Q96, (Qiagen, Valencia, CA, USA).[12]

RESULTS

From April 8 to May 8, 2010, six patients with 2009 H1N1 required mechanical ventilation in the MICU. Five out of these six patients were treated with IV zanamivir. One patient was not treated with IV zanamivir, as he was clinically improving with the use of oral oseltamivir and did not have high nasogastric aspirate to indicate poor absorption. Table I shows the details of these five cases, which are discussed below. Only clinical samples from Cases 1, 2 and 5 were sent to the NPHL, as the other two cases were transferred from other hospitals.

Case 1 was a 44-year-old Chinese man with a history of transient ischaemic attack and childhood asthma. The patient was admitted on April 8, 2010 after one week of fever and cough. Chest radiography on admission revealed bilateral alveolar infiltrates. He was started on ceftriaxone and clarithromycin. His respiratory status deteriorated on Day 3 of hospitalisation, and he required mechanical ventilation in the MICU. His throat swab on that day was positive for 2009 H1N1 by PCR. He was started on oral oseltamivir. Although the dose of oseltamivir was increased to 150 mg twice daily on Day 4 of hospitalisation, high gastric aspirates were noted and poor enteric absorption was a concern. Hence, IV zanamivir 600 mg, 12-hourly was initiated on Day 5 of hospitalisation. His oxygenation status further deteriorated, and high frequency oscillation ventilation

was initiated on Day 9 of hospitalisation. The patient developed multiorgan failure with septic shock, and despite very aggressive measures, including the use of venoarterial extracorporeal membrane oxygenation (ECMO), he died on Day 11 of hospitalisation. This was after completing six days of IV zanamivir.

Case 2 was a 36-year-old Chinese man with no comorbidities. He was admitted on April 16, 2010 after five days of fever and cough. The patient deteriorated within 24 hours of admission and required mechanical ventilation for respiratory failure and shock. Venoarterial ECMO was initiated on the same day for shock and ARDS. His throat swab on the following day was positive for 2009 H1N1 by PCR. Oseltamivir was initiated on the same day at 150 mg, 12-hourly, to be delivered via a nasogastric tube. This was changed to IV zanamivir at 600 mg, 12-hourly on Day 5 of hospitalisation, but the dosage was subsequently reduced to 250 mg, 12-hourly as the patient had acute kidney injury. He received IV zanamivir for five days. His clinical course was complicated by bleeding into the pericardial cavity, resulting in cardiac tamponade. He required thoracotomy and subsequent sternotomy, and also received dialysis for acute renal failure and antifungal treatment for candidaemia. The patient improved clinically, and ECMO was explanted on Day 7 of hospitalisation. He was extubated on Day 13 of hospitalisation and discharged well with serum creatinine at 98 µmol/l after 31 days of hospital stay.

Case 3 was a 47-year-old Malay woman with multiple drug allergies, hypertension and newly diagnosed diabetes mellitus. She was admitted to another hospital on April 20, 2010 due to two days of fever, cough and shortness of breath. The patient developed respiratory failure and hypotension, requiring inotropic support and mechanical ventilation within 24 hours. She was started on antibiotics and oseltamivir empirically. She was then transferred to our MICU to initiate ECMO. Endotracheal aspirate sample collected from Day 1 of hospitalisation at the first hospital was positive for 2009 H1N1. The dose of oseltamivir was increased to 150 mg, 12-hourly on Day 3 of hospitalisation. This was switched to IV zanamivir 600 mg, 12-hourly on Day 4 of hospitalisation. The patient completed five days of IV zanamivir. She also had myocarditis, as evidenced by an elevated Troponin T level and an echocardiogram that revealed an ejection fraction of 20%. During the course of hospitalisation, the patient developed ventilator-associated pneumonia and received broad-spectrum antibiotics. ECMO was explanted on Day 9 of hospitalisation, and she was extubated on Day 15 of hospitalisation. She was discharged well after 22 days of hospitalisation.

Case 4 was a 42-year-old man from Bangladesh who had no comorbidities. He had been admitted to another hospital on April 30, 2010 for a two-week history of fever, cough, abdominal discomfort and mouth ulcers. He required mechanical ventilation for respiratory failure within 24 hours of admission. Throat swab taken on Day 2 of hospitalisation was positive for 2009 H1N1. Oral oseltamivir was started on the day of admission. He developed ARDS and was transferred to our MICU on Day 4 of hospitalisation for ECMO support. He was switched to IV zanamivir 600 mg, 12-hourly the following day due to high nasogastric aspirates. He received IV zanamivir for a total of five days. On Day 8 of hospitalisation, the patient developed ventilator-associated pneumonia, with multidrug resistant *Acinetobacter baumannii*. He was treated with IV polymixin B and nebulised colistin. Subsequently, the patient developed acute kidney injury not requiring dialysis. He also developed pulmonary haemorrhage, which was consistent with haemorrhagic pneumonitis due to 2009 H1N1. ECMO was explanted on Day 11 of hospitalisation and he was extubated on Day 18 of hospitalisation. He was discharged well with serum creatinine at 190 µmol/l after 25 days in hospital.

Case 5 was a 66-year-old Chinese man who had been hospitalised since Feb 13, 2010. The patient had ischaemic heart disease, hypertension and hyperlipidaemia. He was diagnosed with systemic lupus erythematosus (SLE) during admission and received high-dose immunosuppressants for SLE nephritis and central nervous system involvement. He was also treated for cytomegalovirus polyneuropathy and hospital-acquired pneumonia. He was improving and undergoing rehabilitation when he developed acute shortness of breath, fever and cough on May 3, 2010. Bronchoscopy conducted two days later showed pulmonary haemorrhage. Bronchoalveolar fluid was positive for 2009 H1N1 by PCR. The patient was initiated on IV zanamivir 600 mg, 12-hourly on Day 4 of symptoms due to concerns about poor oral absorption from hypoalbuminaemia (serum albumin 18 g/l). The dose of IV zanamivir was changed to 400 mg, 12-hourly, as the patient's calculated creatinine clearance was 48 ml/min. He was intubated for four days and received a total of five days of IV zanamivir. He was discharged on June 4, 2010 with serum creatinine at 63 µmol/l.

IV zanamivir was well tolerated in all the patients; it was also not prematurely stopped in any of the patients due to perceived toxicity. Bleeding was reported in Cases 2 and 4. This was likely related to the use of heparin in ECMO. The viral sequence from Case 1 had a subpopulation that carried the H275Y mutation.

DISCUSSION

We report our experience with IV zanamivir in five severe cases of 2009 H1N1 pneumonia. Apart from Case 5, all patients had received oral oseltamivir prior to receiving IV zanamivir. Case 1 was the first patient to receive IV zanamivir in our hospital. He was a very sick MICU patient who had a large volume of nasogastric aspirates, signifying intolerance to enteral feeding. The H275Y mutation was seen only in a subpopulation of viruses from Case 1. This is known to confer resistance to oseltamivir. The Department of Infectious Diseases and MICU staff were notified as soon as the results were available; however, there was a lag time of 3–5 days before these results were known. As such, concerns regarding resistance to oseltamivir played a role in the choice of IV zanamivir over oral oseltamivir in the subsequent cases of 2009 H1N1 pneumonia seen in the MICU.

Several recent reports have documented the successful use of IV zanamivir. Dulek et al[13] reported its use in an 18-month-old baby who developed respiratory failure from 2009 H1N1 infection while undergoing a bone marrow transplant. The use of zanamivir was considered, as persistent viral shedding and clinical deterioration occurred while the patient was on oseltamivir (this concern about oseltamivir resistance was subsequently proven when the patient's isolate was sequenced). Although this patient did not survive,[13] Gaur et al reported a child with acute leukaemia infected with 2009 H1N1 pneumonia who was successfully weaned off the ventilator after IV zanamivir was started.[14] In the latter case, IV zanamivir was initiated, as the persistently isolated virus was found to contain populations of oseltamivir-sensitive and oseltamivir-resistant viruses. Apart from concerns about oseltamivir resistance, questions about its absorption had also led to its substitution with IV zanamivir. Harter et al used IV zanamivir in two ICU patients due to concerns about oseltamivir absorption in critically ill patients with "presumed reduced perfusion of the gastrointestinal tract and reduced gastrointestinal motility".[15]

In Case 1, the use of IV zanamivir was prompted by the patient's high volume of nasogastric aspirates. Although the use of parenteral agents is prudent and necessary in an ICU patient with large-volume nasogastric aspirates, one study has shown that the bioavailability of oseltamivir in critically ill individuals receiving oseltamivir by nasogastric tube was adequate. However, no mention was made of its gastrointestinal function. In addition, 11 of the 41 patients did not require tube feeding at the time of that study.[16] However, in another study, Wildschut et al reported a significant reduction in oseltamivir absorption in one of the three critically ill children on ECMO. This was attributed to decreased gastric motility, as the patient had gastric bleeding.[17]

While concerns about oseltamivir absorption in the critically ill had caused the attending physicians in our study to lean toward IV zanamivir, concerns about oseltamivir resistance were real. As H275Y mutation was seen in a subpopulation of viruses from Case 1 and the patients had appeared in the MICU sequentially within a short duration of time, there was a lower threshold in using IV zanamivir in subsequent cases owing to concerns of resistance. Peramivir, an NA inhibitor that is available in the IV form, is not yet approved by the US Food and Drug Administration. It has similar efficacy compared to oral oseltamivir, but is not recommended for oseltamivir-resistant viruses.[18,19]

All patients received broad-spectrum antibiotics despite confirmation of the H1N1 infection and the lack of positive bacterial cultures in the clinical specimens. Procalcitonin or C-reactive protein was not used as a surrogate marker for bacterial infections. The antibiotics had likely been prescribed by the attending clinicians, as these patients were critically ill. ECMO had been initiated early in the therapy so as to provide cardiopulmonary support while allowing time for recovery and treatment of the underlying disease process. Bleeding complications occurred in Cases 2 and 4, but these were quickly resolved. Acute renal impairment in the cases was not related to IV zanamivir, as the patients were septic and had hypotension. The renal function in Cases 2 and 4 improved.

Tropical countries such as Singapore experience influenza all year round. There is, however, a bimodal increase in incidence between April to July and November to January, corresponding to the rainy season as well as peak influenza activities in the Southern and Northern hemispheres.[25,26] By March 2010, the pandemic 2009 (H1N1) influenza A activity had declined.[22] Hence, this series of severely ill patients with 2009 H1N1 infection was striking, and illustrates the need to be vigilant. Our case series involved severely ill patients who presented consecutively over a period of one month, which corresponds to the onset of increased influenza activity in Singapore.[21,23]

In conclusion, this case series extends the knowledge regarding the use of IV zanamivir in critically ill patients infected with H1N1 in the absence of real-time access to results for oseltamivir resistance. It represents the tip of the iceberg during the period of increased influenza activity.

ACKNOWLEDGEMENTS

We would like to thank Meng Shu, Phauh Shiau Pheng and Teo Meng Li for their contributions to the technical works in the National Public Health Laboratory, Ministry of Health, Singapore.

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