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ORIGINAL ARTICLE

Effects of corticosteroid and neuraminidase inhibitors on survival in patients with respiratory distress induced by influenza virus

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Abstract *Background/Purpose:* Neuraminidase inhibitors (NAIs) including oseltamivir and peramivir are used for influenza treatment. A systemic corticosteroid is usually administrated for acute respiratory distress syndrome. The aim of this study was to investigate the effect of a systemic corticosteroid and its interaction with NAIs in patients with influenza infection and respiratory distress.
Methods: A retrospective survey of hospitalized patients infected with influenza from January 2012 to May 2014 was conducted in a medical center in Taiwan.
Results: Eighty-six patients were hospitalized during the study period. Forty-eight patients had respiratory distress and 39 of them (81.3%, 39/48) were supported by a mechanical ventilator. All patients with respiratory distress received oseltamivir; 60.4% (29/48) and 31.3% (15/48) of them received a corticosteroid and salvage intravenous peramivir, respectively. All-cause mortality was 29.1% (14/48), 20% (3/15), and 31% (9/29) in patients with respiratory distress, patients who received salvage peramivir, and patients who received a systemic corticosteroid, respectively. Salvage peramivir seemed to improve prognosis in patients with H1pdm09 or type B virus infection and respiratory distress ($p = 0.05$). Early initiating corticosteroid had a worse prognosis than initiation after 72 hours of NAI treatment ($p = 0.024$). In particular, a systemic

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corticosteroid seemed to lead to a shorter survival time in patients with chronic lung disease ($p = 0.05$).
Conclusion: Salvage peramivir provided a better prognosis than monotherapy with oseltamivir in patients who were infected with H1pdm09 or type B virus and who developed respiratory distress. A systemic corticosteroid should be administered after initiating NAI therapy, especially in patients with chronic lung disease.

Introduction

The pandemic H1pdm09 virus spread in 2009 and has been prevalent since 2011. Clinical trials investigating the early use of multidose intravenous peramivir against seasonal influenza including H1N1, H3N2, and type B viruses showed similar outcomes to daily oseltamivir.[1,2] Intravenous peramivir was shown to be effective for the influenza virus infection with the H275Y mutant strain.[3] Emergency use of peramivir has been authorized in the USA since 2009[4] according to the high morbidities and morbidities related to H1N1 (2009) infection. After 2009, only a few reports on the treatment outcomes of peramivir against H1N1pdm09-related infection have been published,[1,5–7] and recent data regarding the clinical outcomes of salvage peramivir for influenza infection with respiratory distress is lacking.

Meanwhile, the benefits of medium-to-high doses of corticosteroid in patients with influenza virus infection and acute respiratory distress syndrome remain controversial.[8] Despite the facts that a corticosteroid is not recommended by some guidelines,[9] it remains standard treatment for physicians working in critical care units to treat acute respiratory distress syndrome[10] after influenza infection.

The newly emerged mutant H275Y strain has been detected in Taiwan,[11] and the use of peramivir was authorized by the Center of Disease and Infection of Taiwan in late 2013 for patients with severe illness who do not respond to oseltamivir. In this study, we aimed to investigate retrospectively clinical outcomes among patients hospitalized with influenza virus infection from 2012 to 2014 in northern Taiwan, and to assess the interaction between two types of neuraminidase inhibitors (NAIs) and administration of a systemic corticosteroid.

Methods

Patients

Patients with laboratory confirmed influenza virus infection from January 1, 2012 to May 31, 2014 in Taipei Veterans General Hospital, Taipei, Taiwan were assessed retrospectively by chart review. Only patients who were older than 18 years and hospitalized were included. Patients with hospital acquired influenza virus infection and contact history were excluded. Clinical characteristics, comorbidities, chest radiography results, laboratory results, and clinical outcome were recorded.

Laboratory confirmation of influenza virus

Confirmation of influenza infection was performed by using a rapid influenza antigen test (Directigen EZ Flu A+B test; BD, Franklin Lakes, NJ, USA) or real-time reverse-transcription polymerase chain reaction (RT-PCR). The primers and Taqman probes used for RT-PCR were those reported in the standard protocol of the Center of Disease Control of Taiwan, which was modified from that of the World Health Organization.[11–13] This protocol includes primers for the matrix gene of influenza A and B viruses, as well as the hemagglutinin gene of influenza A viruses (seasonal H1, H1pdm09, and H3 primers). If the presence of influenza A virus was detected, a further genotype was identified according to the RT-PCR results, i.e., seasonal H1, H1pdm09, or H3; otherwise, unidentified influenza A was recorded.

Medical treatment

The antiviral treatments were according to the manufacturer's guidance: 5 mg of zanamivir powder was inhaled twice daily for 5 days, or 75 mg of oral oseltamivir was given daily for 5 days. Intravenous peramivir was prescribed as 300–600 mg (adjusted by creatinine clearance rate) per 12 hours for at least 3 days, and extended to 5–10 days if clinical symptoms were not completely resolved. Medium-to-high dose corticosteroid was defined as systemic administration of a dose $\geq$ 0.5–2 mg/kg/d.

Clinical manifestations and outcomes

Respiratory distress was defined as desaturation with a ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2/FiO_2) of $<$ 200 mmHg or an oxygen saturation (SaO_2) $<$ 90% with a $FiO_2 >$ 50%. The incidence of organ dysfunction including shock, hematological abnormality (white blood cell count of $>$10,000 cells/mm^3 or $<$ 4000 cells/mm^3, or thrombocytopenia of $<$ 8000 cells/mm^3), respiratory distress, acute disturbance of consciousness levels, acute renal distress with renal replacement therapy, and hepatic failure with decomposition was recorded. The metabolic syndrome was defined according to the World Health Organization[14] and included type 2 diabetes, hyperlipidemia or hypercholesterolemia, cardiovascular disease (including hypertension), and obesity (body mass index $>$ 30 kg/cm^2). Late onset superinfection and colonization were defined as laboratory evidence of