Short Communication

Virological Clearance Rate of High-Dose Oseltamivir or Triple-Combination Antiviral Therapy in Complicated 2009 Pandemic Influenza A (H1N1) Infection

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SUMMARY: The 2009 pandemic influenza A (H1N1) was a considerable public health concern worldwide. Significant morbidity and mortality were observed in complicated cases, despite the early administration of neuramidase inhibitors. The limitations of neuramidase inhibitor monotherapy have renewed interest in combination antiviral therapy or higher-dose oseltamivir therapy. Herein, we report our clinical experience and virological outcomes with high-dose oseltamivir or combination antiviral therapy in seriously complicated 2009 pandemic influenza A (H1N1) infection. Eight patients were treated with high-dose oseltamivir (150 mg twice a day), and 6 patients were treated with triple combination antiviral drugs (150 mg oseltamivir twice a day, 100 mg amantadine twice a day, and 300 mg ribavirin three times a day). Nine of 14 patients (64%) developed acute respiratory distress syndrome and 6 (43%) required mechanical ventilation. Viral clearance was obtained in 9 of 12 patients (75%) after 5 days of antiviral therapy. Two patients died within 5 days of antiviral therapy. The overall mortality rate was 29% (4/14).

In the era of 2009 pandemic influenza A (H1N1) infection, several studies have demonstrated significant morbidity, mortality, or prolonged viral shedding in complicated cases or in immunosuppressed patients, despite the early administration of neuramidase inhibitors (e.g., oseltamivir, zanamivir, and peramivir) (1). In addition, oseltamivir-resistant viruses have been frequently reported during the treatment of such patients (2,3), suggesting the need for other treatment options. Therefore, some experts have recommended that higher doses (150 mg oseltamivir twice a day) of antiviral treatment should be administered in severe cases of 2009 pandemic influenza A (H1N1) infection (4). However, clinical data are lacking to substantiate this recommendation. The limitations of neuramidase inhibitor monotherapy for severe influenza illness have also renewed interest in combination antiviral therapy (5–8). Previous studies have demonstrated that triple combination of antiviral drugs (TCAD)—amantadine, ribavirin, and oseltamivir—was highly and synergistically effective against influenza A virus in vitro, even for drug-resistant strains (6). In a recent study, TCAD impeded the selection of drug-resistant influenza A in vitro (9). However, clinical data on the efficacy of TCAD remain scarce (10,11). Furthermore, no studies have evaluated the virological outcomes of TCAD. Herein, we report

our clinical experience with high-dose oseltamivir and TCAD in seriously complicated 2009 pandemic influenza A (H1N1) infection.

We identified 37 adults (≥ 15 years old) with complicated 2009 pandemic influenza A (H1N1) infection at Chonnam National University Hospital and Chonnam National University Hwasun Hospital (Republic of Korea) between July 2009 and January 2010. The diagnosis of 2009 pandemic influenza A (H1N1) infection was made by reverse transcription-polymerase chain reaction (RT-PCR) assays using specimens from nasopharyngeal/oropharyngeal swabs, sputum, or transtracheal aspirate. RT-PCR was subsequently performed 5 days after antiviral therapy to evaluate viral clearance in respiratory secretions. Real-time RT-PCR or multiplex RT-PCR was performed according to the World Health Organization (WHO) recommendations (12) using the AccuPower New Inf A (H1N1) and Inf A real-time RT-PCR kit (SIA-1111; BIONEER, Daejeon, Korea), which shows similar sensitivity to conventional PCR (13), and Seeplex Influenza A/B OneStep Typing (Seegene, Seoul, Korea). Oseltamivir resistance was tested in patients who had died before completing 5 days of antiviral therapy or who had prolonged viral shedding. Neuramidase sequence analyses for oseltamivir resistance were performed at Korea Centers for Disease Control and Prevention.

Among the 37 patients, 14 with more serious infection were identified. Eight patients were treated with high-dose oseltamivir (150 mg twice a day), and 6 patients were treated with TCAD (150 mg oseltamivir twice a day, 100 mg amantadine twice a day, and 300 mg ribavirin three times a day). The clinical characteristics and

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Table 1. Patients treated with high-dose oseltamivir (150 mg twice per day)

Patient no.	Sex	Age	Charlson comorbidity score	Comorbidity	Pneumonia	ARDS	ICU	Mechanical ventilation	Persistent virus detection	Adverse drug events	14-day outcome	90-day outcome
1	M	76	3	Lymphoma, COPD	Right lobe	No	No	No	Yes	No	Alive	Alive
2	F	78	1	Dementia	Bilateral	No	No	No	No	No	Alive	Alive
3	F	65	1	Old CVA	Bilateral	No	No	No	No	No	Alive	Alive
4	F	16	0	—	Right lobe	No	No	No	No	No	Alive	Alive
5	F	65	0	—	Right lobe	Yes	Yes	Yes	No	No	Alive	Alive
6	F	34	1	Pregnancy 26 weeks, GDM	Bilateral	Yes	Yes	No	No	No	Alive	Alive
7	M	74	2	COPD, DM	Bilateral	Yes	Yes	Yes	—	No	Died	Died
8	F	49	0	—	Bilateral	Yes	Yes	Yes	—	No	Died	Died

ARDS, acute respiratory distress syndrome; ICU, intensive care unit; COPD, chronic obstructive lung disease; CVA, cerebrovascular accident; DM, diabetes mellitus; GDM, gestational diabetes mellitus.

Table 2. Patients treated with triple combination antiviral drugs (amantadine, ribavirin, and oseltamivir)

Patient no.	Sex	Age	Charlson comorbidity score	Comorbidity	Pneumonia	ARDS	ICU	Mechanical ventilation	Persistent virus detection	Adverse drug events	14-day outcome	90-day outcome
9	F	49	0	—	Bilateral	No	No	No	No	No	Alive	Alive
10	F	70	1	Old CVA	Bilateral	Yes	No	No	Yes	No	Alive	Alive
11	F	86	1	COPD	Left lobe	Yes	No	No	Yes	No	Died	Died
12	F	50	2	COPD, DM	Bilateral	Yes	Yes	Yes	No	Hemolytic anemia	Alive	Alive
13	F	27	0	—	Bilateral	Yes	Yes	Yes	No	No	Alive	Alive
14	F	30	1	Pregnancy 28 weeks, GDM	Bilateral	Yes	Yes	Yes	No	No	Alive	Died

Abbreviations are in Table 1.

treatment outcomes of these patients are summarized in Tables 1 and 2. The mean age $\pm$ standard deviation of the patients treated with high-dose oseltamivir or TCAD was 54.9 ± 21.8 years, and 86% (12/14) were female. Medical comorbidity was documented in 9 of 14 patients (64%). Nine of 14 patients (64%) developed acute respiratory distress syndrome and 6 (43%) required mechanical ventilation. Viral clearance was obtained in 9 of 12 patients (75%) after 5 days of antiviral therapy. Two patients died within 5 days of antiviral therapy. Therefore, viral clearance after 5 days of therapy was not determined in these patients. Of the 4 (29%) patients who died, 2 had been treated with high-dose oseltamivir and 2 had been treated with TCAD. No oseltamivir resistance was detected in the patients who died before completing 5 days of therapy or in the patients in whom the virus persisted after 5 days of antiviral therapy. Hemolytic anemia was observed in 1 patient on the third day of TCAD therapy. This patient's hemoglobin content acutely decreased from 11.1 g/dL to 7.9 g/dL within 48 h. This appeared to be an adverse drug event related to ribavirin because no other possible cause of hemolytic anemia was evident. The administration of ribavirin was discontinued after 2 days of use in response to the development of hemolytic anemia.

The present study suggests that high-dose oseltamivir and TCAD could be useful to achieve virological clearance and may be well tolerated for the treatment of complicated 2009 pandemic influenza A (H1N1) infection. In previous studies, the rate of persistent viral shedding in all hospitalized patients ranged from 25–37% (14,15). Ling et al. (14) reported prolonged viral

shedding in 37% of patients treated with a standard dose (150 mg/day) of oseltamivir, and Giannella et al. (15) reported prolonged viral shedding in 25% of patients. The persistent viral shedding was paradoxically higher in patients treated with a higher dose of oseltamivir (300 mg/day; 43%) than in patients treated with a standard dose of oseltamivir (17%) because more serious and immunocompromised patients received a higher dose of oseltamivir. In contrast to a previous study of high-dose oseltamivir therapy (15), the rate of persistent viral shedding in our cases (25% overall; 17% in the high-dose oseltamivir group, and 33% in the TCAD group) was relatively low despite the fact that our study included a similar proportion of seriously ill patients (64% of patients with acute respiratory distress syndrome and 43% with mechanical ventilation).

High doses of oseltamivir have been recommended by some experts for severe cases of 2009 pandemic influenza A (H1N1) infection (4). Although there are concerns regarding possible neuropsychiatric reactions to high-dose oseltamivir (16), a high dose has generally been found to be safe (17). Several reports noted that severely ill patients may benefit from high-dose oseltamivir therapy (18–21). There were no adverse events related to high-dose oseltamivir in the present study. Although this study included a very small number of patients, the data suggest that high-dose oseltamivir could be useful and safe for the treatment of critically ill patients with 2009 pandemic influenza A (H1N1) infection.

Previous studies demonstrated that TCAD was highly and synergistically effective against influenza A virus in vitro, even for drug-resistant strains (6). Regarding TCAD, Kim et al. (11) reported lower 14- and 90-day

mortalities in a TCAD group than in an oseltamivir monotherapy group (17% versus 35% and 46% versus 59%, respectively). However, the virological clearance in each group was not evaluated, and the differences in mortality were not statistically significant. In our study, the mortality of the TCAD group was 17% after 14 days and 33% after 90 days, which was consistent with previous studies of critically ill patients with 2009 pandemic influenza A (H1N1) infection who received oseltamivir or zanamivir (17–41%) (22,23). These data suggest that the mortality rates in critically ill patients treated with TCAD were comparable with those in patients treated with oseltamivir or zanamivir monotherapy. Considering that these studies were retrospective in design and included patients with several underlying diseases and complicated illnesses, a prospective controlled study is warranted to ensure accurate evaluation of the efficacy of TCAD.

In conclusion, our data suggest that TCAD and high-dose oseltamivir could be useful to achieve virological clearance and can be considered as alternative treatment options for serious 2009 pandemic influenza A (H1N1) infection.

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Conflict of interest None to declare.

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