Case Report

Do Immunosuppressive Patients Really have a Severe Outcome with H1N1 Virus Infection?

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Summary
Influenza virus is a common human pathogen that has the potential to cause widespread pandemics. The last pandemic began in April 2009 in CA, USA and killed about 14,000 people since then. The virus affects people at all ages, and school-aged children have the highest rates of infection. Chronic lung disease, immunosuppression and pregnancy are risk factors for seasonal influenza and pandemic influenza as well. Here, we report five immunosuppressive patients due to various diseases infected with H1N1 influenza and who were completely revealed after promptly treatment with oseltamivir.

Key words: H1N1, Infection, immunosuppression.

Introduction
Influenza virus is a common human pathogen that has the potential to cause widespread pandemics [1, 2]. It is highly contagious, affects people at all ages and has a particularly profound effect on children. School-aged children have the highest rates of infection [3–5]. The virus caused serious respiratory illness and death over the past century [2].

When minor antigenic variations occur (antigenic drift), epidemics are seen and pandemics occur when major variations emerge (antigenic shift) [5]. During the 20th century, there were three influenza pandemics: the first one in 1918 (Spanish flu) killed >20 million people worldwide, many of whom were young adults. Mortality rates with the pandemics of 1957 and 1968 were lower in part because of the use of anti-microbial therapy for secondary bacterial infections [5].

The last pandemic began in April 2009. Center of Disease Control (CDC) reported for the first time that a new strain of swine flu virus had infected two children in CA, USA. Since then the virus spread rapidly worldwide. This H1N1 virus had a genetic composition quite different from the earlier known isolates [2]. The World Health Organisation (WHO) declared the first flu pandemic since 1968 and raised the alert level to Phase 6 on 11 June 2009 [2, 3]. The WHO reported approximately 14,142 deaths since 1 January 2010; almost all of them were laboratory confirmed cases of infection. The first case in Turkey was diagnosed on 17 May 2009. He was a tourist travelling from USA to Iraq. Since then 100 cases of death were declared by the Ministry of Health in Turkey.

Observations have suggested that most infections occur in young individuals, with 40% between 10 and 18 years and 95% <50 years. Chronic lung disease, immunosuppression and pregnancy are risk factors for seasonal influenza and these also appear to be at risk for pandemic 2009 influenza [3]. Immunosuppressed patients are also at increased risk for more severe and prolonged infection [6].

Here, we report five immunosuppressive patients due to various conditions and infected with H1N1 influenza and treated successfully with oseltamivir.

Case Reports

Case 1
A 10-year-old girl was admitted to the hospital with fever and cough. She had been followed up with the diagnosis of mixed connective tissue disease (MCTD) for 4.5 years on methotrexate and prednisolone therapies, and started on etanercept before 1 year. Physical examination was normal except tonsillo-pharyngitis. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were slightly elevated. Real-time reverse transcriptase polymerase
therapy. She was discharged with her own therapy protocol.

Case 2
A 10-year-old boy was admitted to the hospital with fever lasting for 2 days. He had been followed up with the diagnosis of focal segmental glomerulosclerosis (FSGS) for 5 years and was on the treatment with high-dose oral prednisolone for 5 weeks because of disease recurrence. On physical examination, he had pharyngeal hyperaemia. Chest X-ray was normal. ESR and CRP were slightly elevated. RT-PCR was positive for H1N1. Oseltamivir was started and oral steroid treatment was discontinued. Fever subsided after the third day of therapy and he was completely well at the end of the 5 days.

Case 3
A 13-year-old boy, who had been followed up with the diagnosis of familial Mediterranean fever (FMF), was admitted to our hospital because of long-lasting fever and arthralgia on his elbows. He had been suffering from recurrent attacks of vasculitis each of which was treated with prednisolone for 7 years. He was treated with pulse methyl prednisolone (30 mg kg\(^{-1}\) day\(^{-1}\) for 3 days) with the diagnosis of vasculitic recurrence and relief of his symptoms in 2 days. However, he developed fever and sore throat 2 days after this therapy. Chest X-ray was normal, acute-phase reactants were markedly elevated and RT-PCR was positive for H1N1. Oseltamivir was started and oral steroid treatment was discontinued. Fever subsided after the third day of therapy without any complication. He was discharged after the seventh day with his previous therapy protocol.

Case 4
A 14-year-old girl was admitted to our clinic with fever, sore throat, nausea and vomiting lasting for 1 day. She had been followed up with the diagnosis of systemic lupus erythematosus (SLE) being on the treatment with azathioprine and low-dose oral prednisolone for 5 years. Her physical examination revealed pharyngeal hyperaemia. CRP and ESR were slightly elevated, chest X-ray was normal and RT-PCR was positive for H1N1. She was started on oseltamivir treatment with cessation of immunosuppressive drugs. Her symptoms relieved in 48 h and she was completely well at the fifth day of treatment. She was discharged with her own therapy.

Case 5
A 4-year-old girl was admitted to the hospital with arthritis on her knees for lasting about 1 year. After clinical and laboratory examinations she was diagnosed as juvenile idiopathic arthritis (JIA) and was started on methotrexate and oral prednisolone. On the second week of methotrexate therapy she developed fever, nausea and vomiting. ESR and CRP were slightly elevated, chest X-ray was normal and RT-PCR was positive for H1N1. Oseltamivir was started, immunosuppressive therapy was discontinued and her symptoms subsided after 48 h of therapy. She was well at the end of the first week and her immunosuppressive therapy was restarted.

Discussion
According to CDC reports, most infections occur in younger individuals; 95% of cases being <50 years and 40% of them between 10 and 18 years [7]. Unlike seasonal influenza, people >65 years are less susceptible probably due to cross-protection from pre-existing antibodies for swine-origin influenza infection (S-OIV) [3, 8]. Louie et al. [3] reported that the median age of all cases was 27 years (range <1 to 92 years). According to this report, hospitalization rates were highest in infants <1 year and were higher among the people >70 years. Although H1N1 infections are less common in this age group, fatality rates are higher than the youngsters [3]. There are also other conditions that increase the susceptibility to H1N1 pandemic infection as in seasonal influenza: pregnancy, chronic heart or lung disease, metabolic or renal disease, haematopoetic stem cell and solid organ transplant recipients, congenital immunodeficiencies, autoimmune conditions, chronic corticosteroid use and cancer chemotherapy [6, 9–11]. However, the prognosis of the infection in those patients with high risk is not well known yet.

All our patients were at the risk group because of their underlying conditions such as MCTD, FMF, FSGS, SLE and JIA. Besides the course of their diseases, the therapeutic agents they were receiving also increased their tendency to infection as well as the severity of the disease. Three of the patients were at chronic corticosteroid use (Cases 1, 2 and 4), three of them used other immunosuppressive medications (Cases 1 and 5 methotrexate and Case 4 azathioprine) and Case 3 had just been administered pulse methyl prednisolone before the infection. However, all the patients recovered in short time with immediate oseltamivir therapy.

Although all our patients had fever and typical symptoms of influenza, it is known that severely immunosuppressive patients may not develop fever at the beginning of the disease [6]. Therefore, clinicians should suspect H1N1 influenza in these patients with acute respiratory symptoms with or without fever. Respiratory specimens should be sent to laboratory.
as soon as possible and empiric anti-viral treatment must be started without waiting for laboratory confirmation [6, 12]. All of our patients were admitted to the hospital early and were started on oseltamivir treatment immediately after getting the nasal specimens for rt-Rp [13].

Viral shedding may prolong in immunosuppressive patients and resistance to oseltamivir treatment may occur [6, 9, 14]. These patients may be infectious to community for longer time than the otherwise healthy people. Efficacy of early anti-viral treatment (<48 h from illness onset) of previously healthy people has been demonstrated in randomized clinical trials [6]. For seasonal influenza and 2009 H1N1 infection, there are observational studies indicating that initiation of oseltamivir after 48 h of onset is associated with survival benefit compared to no treatment [6]. Due to the mentioned prolonged viral shedding, some experts recommend longer duration of treatment (e.g. 10 days vs. standard 5 days) [6]. Except Case 2, all of our patients were started with oseltamivir in the first 48 h. Case 2 was admitted on the third day of his symptoms, but he was also administered with oseltamivir in the face of his immunosuppression. All of the patients improved shortly after the beginning of the treatment; they were treated for 5 days and there were no complications. Although additional influenza testing is recommended by some experts at the end of the treatment to determine the viral shedding, we could not perform it [6, 14].

In conclusion, although immunosuppressive patients are more susceptible to H1N1 2009 influenza infection and viral shedding is more likely to prolong with more common oseltamivir resistance, the prognosis is not worse in these patients with early diagnosis and treatment.

References