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Oseltamivir-Resistant Novel Influenza A (H1N1) Virus Infection in Two Immunosuppressed Patients — Seattle, Washington, 2009

Novel influenza A (H1N1) virus infection continues to cause illness and death among persons worldwide. Immunosuppressed patients with influenza virus infection can shed virus for prolonged periods, increasing the chances for development of drug resistance (*1–3*). On August 6, 2009, CDC detected evidence of resistance to the antiviral medication oseltamivir in two severely immunosuppressed patients with novel influenza A (H1N1) virus infection in Seattle, Washington. The two patients were treated in two different hospitals, and their cases were not epidemiologically linked. Both were being treated with oseltamivir for novel influenza A (H1N1) virus infection and had prolonged viral shedding. In both patients, the virus was documented as initially susceptible to oseltamivir, and resistance developed subsequently during treatment with the drug. Testing of viral RNA from both patients by pyrosequencing detected a mutation that results in a histidine-to-tyrosine substitution at position 275 (H275Y) in the neuraminidase, known to be associated with oseltamivir resistance (*4,5*). The results were confirmed by pyrosequencing, sequencing of the neuraminidase gene, and neuraminidase inhibition testing of virus isolates on August 11. One patient's symptoms resolved after treatment with oseltamivir, and the other patient was receiving treatment with zanamivir and ribavirin as of August 13. An investigation of health-care personnel (HCP) contacts and other close contacts revealed no evidence of virus transmission. This report summarizes the case histories and resulting investigations and highlights the importance of 1) close monitoring for antiviral drug resistance among immunosuppressed patients receiving treatment for novel influenza A (H1N1) virus infection and 2) the implications for infection control.

Case Reports

Case 1. A teen-aged male was diagnosed with leukemia in November 2008 and subsequently received outpatient immunosuppressive chemotherapy. On April 29, 2009, he was hospitalized for a hematopoietic stem cell transplant, which he received on May 7. He received immunosuppressive treatment prior to his transplantation and remained hospitalized in a single-patient room after the transplantation. On May 31, he developed fever, mild cough, and rhinorrhea, was placed on droplet and contact precautions, and HCP began using respirators (fit-tested N95 or higher-level protection) for his care. A nasal wash specimen collected on May 31 tested positive for novel influenza A (H1N1) virus by real-time reverse transcription–polymerase chain reaction (rRT-PCR) at the University of Washington Virology Laboratory. On June 1, the patient was enrolled in an influenza antiviral treatment study and he began a 10-day course of oseltamivir. However, on June 4, novel influenza A (H1N1) virus was detected again by rRT-PCR and viral culture in nasal wash specimens, and oseltamivir treatment was extended to a 20-day course, to June 20. The patient improved and was discharged to a nearby apartment on June 7. Virus again was detected in nasal wash specimens on June 11. On July 7, a nasal wash specimen collected for routine follow-up on an outpatient basis was positive for novel influenza A (H1N1) virus by rRT-PCR; oseltamivir therapy was resumed on July 8.

The patient remained well until July 14, when he was hospitalized with fever and treated for coagulase-negative staphylococcal infection of an indwelling central venous catheter. A nasal wash specimen collected on July 14 tested positive for novel influenza A (H1N1) virus by rRT-PCR, and his oseltamivir was increased to a high dose, 150 mg orally, twice a day. Increased rhinorrhea and mild cough were noted on July 16. The patient was discharged on oseltamivir on July 18.

Because of prolonged shedding of novel influenza A (H1N1) virus and suspected oseltamivir resistance, nasal wash specimens previously collected from the patient were sent to CDC for antiviral resistance testing and arrived on August 5. On August 6, pyrosequencing at CDC of viral RNA from a specimen collected on June 4 revealed susceptibility to oseltamivir.

However, pyrosequencing of a follow-up specimen collected on July 30 indicated oseltamivir resistance, based on detection of the H275Y mutation (*4,5*). Treatment of the patient with oseltamivir was stopped on August 6, when CDC pyrosequencing results from the specimens became available. Because the patient was asymptomatic, no further treatment was indicated.

On August 10, CDC received previously collected virus isolates from the patient for pyrosequencing on August 11, which confirmed the previous results. A novel influenza A (H1N1) virus isolate from a specimen collected on May 31 was identified as susceptible to oseltamivir by pyrosequencing at CDC, but viruses isolated from specimens collected on June 11 and July 14 had the H275Y mutation, indicating oseltamivir resistance.

Seattle-King County health department investigators interviewed hospital infection-control staff and the patient's family members and visitors. Surveillance for influenza-like illness (ILI) among staff members is standard policy at the hospital where the patient was treated. No cases of ILI were reported among approximately 100 HCP contacts of the patient. Active surveillance, involving personal interviews of HCP contacts during the 2 weeks before diagnosis of oseltamivir resistance did not identify any HCP with ILI.

After each hospital discharge, the patient lived under voluntary home isolation according to standard protocol for patients in the post-hematopoietic stem cell transplant (HSCT) period; he did not attend any school. When traveling in public, the patient reported wearing a surgical mask per protocol for immunosuppressed HCST recipients and avoiding close contact with other persons and crowds. None of the 12 family member contacts or other persons who had visited the patient while he was in isolation reported symptoms of ILI.

Case 2: A female patient in her 40s who had a hematopoietic stem cell transplant for leukemia had a recurrence of leukemia in December 2008. She underwent two cycles of immunosuppressive chemotherapy during March–April 2009. On June 21, she was admitted to the hospital for further chemotherapy; she also had developed a fever and symptoms of an upper respiratory infection. She was placed in a single-patient room with droplet and contact precautions, and a nasal wash specimen was obtained for direct fluorescent antibody staining (DFA) and viral culture. The DFA result was indeterminate because of an inadequate cellular specimen; however, on June 26, the University of Washington Virology Laboratory reported isolation of influenza A virus from the specimen. Antiviral treatment with high-dose oseltamivir (150 mg orally, twice a day) and rimantadine (100 mg orally, twice a day) was administered during June 26–July 1. On July 3, the viral isolate was identified as novel influenza A (H1N1), and high-dose oseltamivir and rimantadine were restarted. The patient's respiratory status worsened, and she required supplemental oxygen for hypoxia. Novel influenza A (H1N1) virus was isolated from additional nasal wash specimens collected on July 6 and July 14, and from bronchoalveolar lavage specimens obtained on July 16 and 28. Because of prolonged viral shedding, specimens were sent to CDC on August 4 for antiviral susceptibility testing. Treatment with inhaled zanamivir was attempted, but was poorly tolerated, and oseltamivir was continued.

On August 6, CDC determined that pyrosequencing of viral RNA from the first clinical specimen collected on June 21 did not detect the H275Y mutation. However, the mutation was detected by pyrosequencing of viral RNA from a nasal wash specimen collected on July 28. Treatment of the patient with oseltamivir was discontinued when results became available.

Treatment with inhaled zanamivir after identification of oseltamivir resistance again was attempted but poorly tolerated. On August 7, intravenous zanamivir, acquired through an emergency investigational new drug application for compassionate use, and aerosolized ribavirin therapy were initiated. As of August 13, the patient remained symptomatic and hospitalized on intravenous zanamivir and had been switched to oral ribavirin because of intolerance of aerosolized ribavirin. The patient's hospital course was complicated by prolonged neutropenia and protracted bone marrow recovery, neutropenic fever, coagulase-negative *Staphylococcus* bacteremia, and *Pneumocystis jirovecii* pneumonia. On August 10, CDC received other previously collected virus isolates from this patient for testing, and pyrosequencing of a virus isolated from a specimen collected on July 14 had the H275Y mutation, confirming oseltamivir resistance.

The patient was hospitalized in a single-patient room upon admission on June 21. She was initially placed on droplet and contact precautions. Immediately after confirmation of novel influenza A (H1N1) virus infection, use of N95 repirators by HCP also was implemented. Active surveillance for respiratory illness among staff members is routine at the hospital where the patient was treated, and no cases of ILI or other acute respiratory illness were reported among the approximately 200 HCP contacts who cared for the patient. No breaches of personal protective equipment recommendations (including use of fit-tested N-95 respirators) were reported among HCP contacts caring for this patient.

Testing of Clinical Specimens for Oseltamivir Resistance

CDC has tested virus isolates or clinical specimens collected from 37 additional Washington residents with confirmed novel

influenza A (H1N1) virus infection during April 26–July 30. None of these viruses had evidence of the H275Y mutation. As of August 11, of the 670 novel influenza A (H1N1) viruses collected since April 2009 in the United States and tested at CDC, 318 had been tested for oseltamivir and zanamivir resistance by neuraminidase inhibition assay, and 352 clinical specimens had been screened for oseltamivir resistance for the H275Y mutation by pyrosequencing. No other oseltamivir-resistant viruses had been identified. Oseltamivir-resistant viruses isolated from both patients described in this report were determined to be susceptible to zanamivir by neuraminidase inhibition assay at CDC. Sequence analysis of the neuraminidase gene of these oseltamivir-resistant viruses showed that oseltamivir resistance was not the result of gene reassortment with seasonal influenza A (H1N1) virus.

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Editorial Note: This report describes oseltamivir-resistant novel influenza A (H1N1) virus infection in two severely immunosuppressed patients who were treated with oseltamivir for acute illness symptoms of laboratory-confirmed influenza. Initially, both patients were infected with oseltamivir-susceptible viruses; oseltamivir resistance developed later during antiviral treatment. The two patients were not epidemiologically linked and were treated at different hospitals. No evidence was found that HCP or other patient contacts developed ILI caused by oseltamivir-resistant novel influenza A (H1N1) virus infection.

Immunosuppressed patients are at increased risk for complications of influenza and are recommended for annual influenza vaccination, although the immune response to vaccination can be decreased in some persons (*6,7*). In otherwise healthy adults with seasonal influenza virus infection, viral shedding generally resolves within 7 days, compared with immunosuppressed patients, who can experience prolonged viral shedding for weeks to months. Antiviral resistance can develop during treatment of influenza in these patients, and prolonged viral shedding (*1,2*) of up to 18 months has been reported, including shedding of oseltamivir-resistant seasonal influenza A virus for more than 1 year (*3*). Clinicians caring for immunosuppressed patients with novel influenza A (H1N1) virus infection should be aware of the potential for development of antiviral drug resistance during therapy and prolonged viral shedding. Recommendations for prevention and control of seasonal influenza among hematopoietic stem cell transplant recipients, their family members, and HCP have been published (*8*). Strict adherence to recommended personal protective equipment and infection-control measures is advised until an immunosuppressed patient with influenza virus infection has serial respiratory specimens that remain negative when tested by both rRT-PCR and viral culture. Interim infection-control guidance for novel influenza A (H1N1) is available on the CDC website.*

Only sporadic cases of oseltamivir resistance associated with the H275Y mutation in the neuraminidase have been detected in immunocompetent persons exposed to oseltamivir (*9*). As of August 11, no evidence had been found of ongoing transmission of oseltamivir-resistant novel influenza A (H1N1) virus in the United States or elsewhere in the world. The public health risk of virus transmission from these two immunosuppressed cases with oseltamivir-resistant novel influenza A (H1N1) virus infection appears to be low. Currently, enhanced surveillance for oseltamivir resistance among novel influenza A (H1N1) virus strains isolated from outpatients and hospitalized patients is being conducted in Washington in collaboration with CDC. The two cases in immunosuppressed patients described in this report and sporadic cases of oseltamivir resistance in persons with oseltamivir exposure, highlight the need for ongoing global virologic surveillance and monitoring of antiviral resistance (*10*).

All circulating novel influenza A (H1N1) virus strains worldwide remain susceptible to oseltamivir and zanamivir but resistant to amantadine and rimantadine. CDC continues to recommend oseltamivir or zanamivir for treatment of all hospitalized patients with suspected or confirmed novel influenza A (H1N1) virus infection and for outpatients at increased risk for influenza-related complications (e.g., young children, pregnant women, and persons with certain chronic medical conditions) with suspected or confirmed novel influenza A (H1N1) virus infection. Novel influenza A (H1N1) virus strains with the H275Y mutation are susceptible to zanamivir. Therefore, in immunosuppressed patients with oseltamivir-resistant novel A (H1N1) virus infection, zanamivir should be considered the antiviral treatment of choice; however, zanamivir is not recommended for persons with underlying airway disease.† Additional interim guidance on the use of antiviral medications for the treatment and prevention of novel influenza A (H1N1) virus infection is available on the CDC website.§

* Available at http://www.cdc.gov/h1n1flu/guidelines_infection_control.htm.
† Available at http://us.gsk.com/products/assets/us_relenza.pdf.
§ Available at http://www.cdc.gov/h1n1flu/recommendations.htm.

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