CORRESPONDENCE

Emergence of Oseltamivir-Resistant Pandemic H1N1 Virus during Prophylaxis

TO THE EDITOR: Neuraminidase inhibitors (oseltamivir and zanamivir) are recommended for treatment of severe illness caused by the 2009 pandemic influenza A (H1N1) virus, and their use has also been advocated for postexposure prophylaxis in high-risk persons.[1] We report the emergence of an oseltamivir-resistant virus in a familial cluster of infections with the 2009 H1N1 virus.

In a 13-year-old boy with asthma, infection with the 2009 H1N1 virus developed and was confirmed by reverse-transcriptase polymerase-chain-reaction (RT-PCR) testing of a nasopharyngeal aspirate. Administration of oseltamivir (60 mg twice a day for 5 days for this boy who weighed 32 kg) was begun, and the patient was discharged home the same day. Simultaneous with treatment of the index patient, postexposure prophylaxis with oseltamivir (75 mg once a day for 10 days) was prescribed to all household contacts (the boy's 59-year-old father, who had chronic obstructive pulmonary disease and was taking prednisone at a dose of 5 mg daily; 50-year-old mother; and 15-year-old and 18-year-old sisters). Approximately 24 hours after oseltamivir prophylaxis was begun, influenza-like symptoms developed in the father (Fig. 1). On day 8 of oseltamivir prophylaxis, the father consulted his general practitioner because of persistent cough. A nasopharyngeal aspirate collected at that time was positive for the 2009 H1N1 virus, according to RT-PCR testing and culture. The father had an uneventful clinical course, and a nasopharyngeal aspirate sampled at the end of his illness was negative for the 2009 H1N1 virus. Influenza-like symptoms did not develop in any other household contacts.

The 2009 H1N1 viral isolate collected from the index patient before oseltamivir therapy was susceptible to oseltamivir (50% inhibitory concentration, 0.27 nM) and zanamivir (50% inhibitory concentration, 0.18 nM), whereas the father's 2009 H1N1 viral isolate was resistant to oseltamivir (50% inhibitory concentration, >400 nM) but susceptible to zanamivir (50% inhibitory concentration, 0.12 nM). Complete 2009 H1N1 virus genomes of the father's virus (GenBank accession number, FN434454) differed from the index patient's virus (GenBank accession number, FN434445) by only one substitution (H275Y) in the neuraminidase protein. The role of the H275Y substitution was assessed by generating recombinant neuraminidase proteins.[2] The mutant neuraminidase protein was more resistant to oseltamivir than was the wild-type protein by a factor of more than 400, confirming the phenotypic results.

Our results indicate that the same neuraminidase mutation (H275Y) is associated with oseltamivir resistance not only in seasonal H1N1[3] and avian H5N1[4] viruses but now also in 2009 pandemic H1N1 strains. We hypothesize that the presence of subtherapeutic levels of oseltamivir at a time when viral replication had already begun was an important factor that led to the emergence of the resistant virus in the father of our index patient. Other oseltamivir-resistant strains of 2009 H1N1 virus detected during postexposure prophylaxis have been reported to the World Health Organization.[5]

These observations support the need for limiting the indications for postexposure prophylaxis. It also seems reasonable to rapidly convert prophylactic (once daily) regimens to therapeutic (twice daily) regimens as soon as influenza-like symptoms develop in a patient receiving prophy-

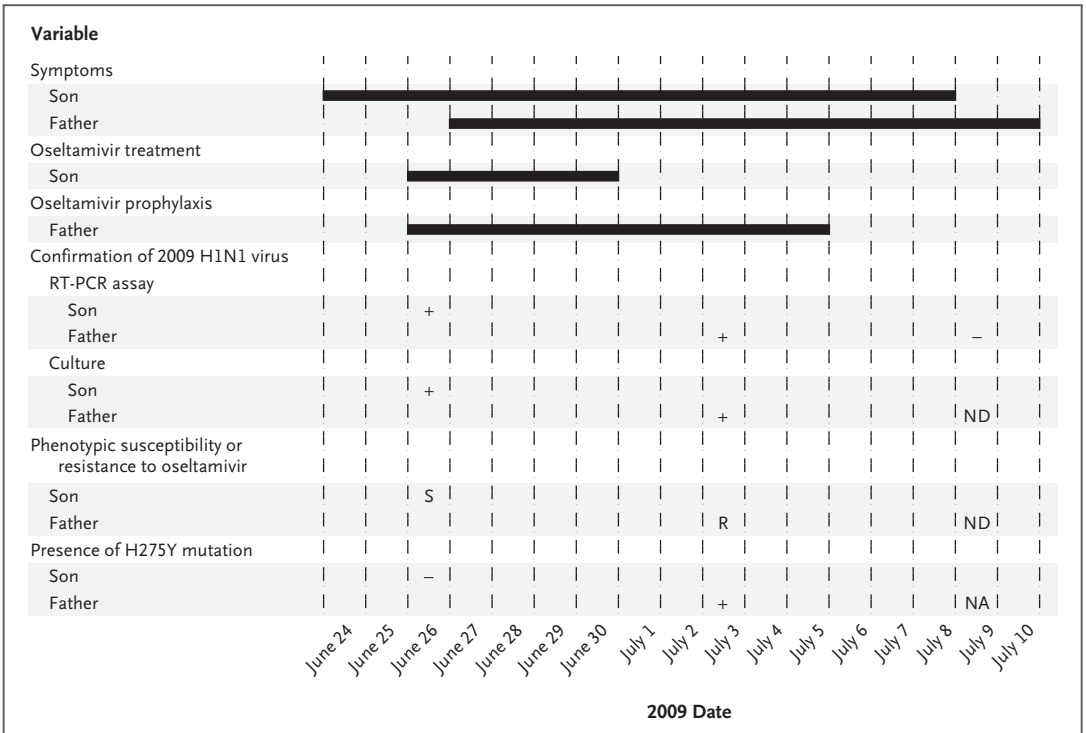

Figure 1. Symptoms, Antiviral Therapy, and Virologic Results in the Index Patient and His Father.

Timelines are shown for the index patient (the son), who was infected with a wild-type strain of 2009 H1N1 virus, and his father, who was infected with a H275Y mutant strain of 2009 H1N1 virus. NA denotes not applicable, ND not done, R resistant, RT-PCR reverse-transcriptase polymerase chain reaction, S susceptible, + positive, and – negative.

lactic treatment. Monitoring for the H275Y mutation during outbreaks of 2009 H1N1 virus is important in order to rapidly identify transmission events that could lead to large-scale dissemination of an oseltamivir-resistant 2009 H1N1 virus, similar to what occurred with recent H1N1 virus seasonal strains.[3]

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