Prolonged oseltamivir treatment for severe influenza pneumonia: Requirement of combination therapies.

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A recent article by Gerard Moreno et al. compared the efficacy of a standard oseltamivir (5 doses) versus a prolonged oseltamivir treatment (10 doses) in critically ill influenza patients admitted into intensive care units (ICUs).[1] Oseltamivir was administered at 75 mg/dose twice daily, and patients were monitored for death or discharge from the hospital as primary outcomes. Overall, this retrospective multicenter cohort study provides valuable insights and important scientific rationale that patients with severe lower respiratory tract influenza infections require extended antiviral therapy to contain the virus shedding in the deeper lungs. However, this study raises several concerns about the limitations of prolonged oseltamivir therapy in ICU patients.

First, although this retrospective study demonstrates the beneficial effects of prolonged oseltamivir treatment, due to the high diversity in influenza virus strains, their persistent mutative ability, and being a most common community-acquired viral pathogen, extreme caution must be taken to avoid unwanted use of extended oseltamivir and prevent the origin of resistant viral strains. Genetic fluctuations of the surface genes of the influenza virus are potent contributors for the origin of resistance *via* antigenic drift or spontaneous mutations[2] and lacking this information is one of the major limitations of this study. Second, prolonged oseltamivir treatment in immunocompromised patients functions as a double-edged sword. It has been reported that immunocompromised patients on chemotherapy, solid organ transplantation, or under corticosteroid therapies take more extended periods for virus clearance.[3-4] Although prolonged oseltamivir treatment will likely yield potent antiviral effect, extended oseltamivir therapy induce spontaneous origin of the oseltamivir-resistant mutant (H275Y) strain in immunocompromised patients.[5] The origin of H275Y mutants was observed within a week when influenza-infected immunocompromised ferrets were treated with oseltamivir.[5] The origin of quick resistance to oseltamivir is truly alarming, as oseltamivir will be the top

choice of antiviral drug used in case of a pandemic outbreak, and there is a high chance for quick origin of the resistant viral strains due to extensive use of this drug. Further, it is not clear whether the proposed prolonged oseltamivir treatment strategy can be applied to other approved antiviral drugs, such as zanamivir, peramivir, or baloxavir in ICU-admitted patients.

Third, it is critical to explore other choices of treatments to overcome the problem of the origin of resistant viral strains. One such alternative is using a combination of two or more antiviral agents.[6-7] Several clinical trials have tested a combination of antiviral agents that target either the same viral protein (ex. neuraminidase, which helps in progeny virus release) or different viral proteins that interfere with different stages of virus infection (viral attachment, replication, or progeny virus release). A combination of antiviral drugs, including oseltamivir plus baloxavir marboxil (inhibitor of cap-dependent endonuclease activity), has shown synergistic effects compared to oseltamivir alone treated patients, but no significant improvements in the clinical outcomes were observed.[8] Similarly, a triple combination antiviral therapy that includes oseltamivir, Amantadine (M2 ion channel inhibitor), and ribavirin (inhibitor of the viral polymerase) yielded promising results as oseltamivir and amantadine also exhibited antiviral activity against resistant viral strain in the combination therapy.[9] However, although the triple combination drugs are well tolerated in the mechanically ventilated critically ill pandemic H1N1 influenza-infected patients, the clinical signatures were comparable with oseltamivir alone treated patients.[10]While treating critically ill influenza patients, it is critical to monitor two additional parameters including superinfections[11] and host-induced immunopathology[12] that could significantly exacerbate pulmonary pathology, thus worsening clinical outcome.

From the history of influenza pandemics since 1918, it is known that secondary bacterial superinfections mainly contributed to devastating mortalities during influenza outbreaks.[11] The failure in the clinical outcome, despite using antivirals and antibiotics in severe influenza, could be due to a lack of proper diagnosis of resistant viruses and bacterial pathogens involved in superinfections. Hence, efforts must be made to strengthen the screening and diagnostic capacities for early detection and rapid onset of antiviral treatment, together with continuous monitoring of secondary bacterial infections for selective antibiotic treatment, especially in patients admitted into ICUs.

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