Parenteral Peramivir Treatment for Oseltamivir-Resistant 2009 Pandemic Influenza A H1N1 Viruses

To the Editor—In a recent issue of the Journal, Memoli and colleagues demonstrated, by using a relevant animal model (ie, ferrets), that viral fitness and transmissibility of 2009 pandemic influenza A H1N1 virus (pH1N1) isolates harboring the H275Y neuraminidase mutation were conserved [1]. Because the H275Y mutation was associated with a high level of resistance to oseltamivir and also conferred an intermediate level of resistance to peramivir [2], and given the fact that pH1N1 strains are naturally resistant to adamantanes, the search for antiviral alternatives against multidrug-resistant pH1N1 variants is highly relevant. In particular, these authors suggested that therapy with peramivir may not be an adequate treatment option in the case of infections with pH1N1 with the H275Y mutation.

Although few currently circulating strains are H275Y mutants [3,4], several lines of evidence suggest that the shift in susceptibility to peramivir in H275Y mutants may not be clinically significant: (1) The intrinsic potency of peramivir against pH1N1 strains is significantly higher [5]; (2) peramivir has a higher binding affinity and slower off rate from neuraminidase than those of oseltamivir carboxylate or zanamivir [6]; and (3) the peak levels achieved after administration of intravenous peramivir at the current dose (~10,000 nmol/L) [7,8] are much higher than the in vitro median inhibitory concentration for resistant isolates [9].

Mouse model data suggest that once daily dosing for 5–10 days may be superior to a single administration of peramivir for H275Y neuraminidase mutants [10]. The prophylactic activity of intramuscular peramivir was evaluated in mice infected with wild-type and H275Y mutant recombinant influenza A/WSN/33 (H1N1) viruses. Regimens used single (45 mg/kg or 90 mg/kg) or multiple (45 mg/kg daily for 5 days) intramuscular injections starting 1 hour before viral challenge. All peramivir regimens prevented mortality and weight loss while significantly reducing lung viral titers (LVTs) in mice infected with wild-type virus compared with untreated control mice. For the H275Y mutant, the multiple-dose regimen prevented mortality and weight loss and was associated with significant LVT reduction compared with untreated animals. Both single-dose regimens also reduced mortality and weight loss but not LVTs. In contrast, in a similar mouse model, prophylactic oral oseltamivir regimens did not prevent mortality or weight loss following infection with the same recombinant H275Y virus [10].

The activity of intravenous peramivir was also evaluated in a similar mouse model with H275Y mutant influenza A/WSN/33 (H1N1) viruses. Peramivir administered as a single intravenous injection improved survival rates in a dose-dependent manner: 40% survival at 20 mg/kg and 100% survival at 100 mg/kg. In contrast, mice administered oral oseltamivir phosphate at 10 mg/kg twice daily for 5 days (100 mg/kg as a total dose) showed 20% survival. Single-dose intravenous treatment with peramivir had strong in vivo therapeutic efficacy against H275Y viruses, despite decreased in vitro inhibitory activity (R. Yoshida et al, unpublished data).

Whether intravenous peramivir is also efficacious in treatment of established infection with H275Y mutant influenza viruses is being evaluated in further experiments. Although the outcome of the single case treated with intravenous peramivir in the emergency investigational new drug series and uncontrolled data in high-risk patients infected with influenza viruses including H275Y mutants [8] are encouraging, controlled human trials are needed to confirm the efficacy of intravenous peramivir against H275Y mutants.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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