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Oseltamivir

A Viewpoint by Shiro Shigeta

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A pandemic of influenza in the near future has been predicted since 18 cases of influenza by an avian-type virus (H5N1) were reported in Hong Kong between 1997 and 1998. In order to prevent the high mortality associated with the newly emerging influenza, clinical investigation has focused on the development of a potent anti-influenza chemotherapy.

Neuraminidase (NA) inhibitors specific for influenza virus NA have been developed and the first inhibitor, zanamivir (previously GG167), has been examined in clinical trials. The results of a double-blind trial were reported and zanamivir was found to be effective for alleviating major influenza symptoms compared with placebo. However, zanamivir has shortcomings in that it must be administered by inhalation because of its poor absorption from the alimentary tract. In general, it is difficult to administer zanamivir to infants and children by inhalation without the use of special equipment.

More recently, a novel orally bioavailable influenza NA inhibitor, oseltamivir (GS4104), has been developed. After absorption from the alimentary tract, oseltamivir is converted to its non-ester form, GS4071, which is distributed efficiently to the lungs and other sites of influenza infection. The absorption ratio of oseltamivir is reported to be 80% of an intravenous injection of GS4071 at the same dose. In contrast, the absorption ratio of zanamivir from the alimentary tract is 3 to 4%.

Development of resistance to NA inhibitors is infrequently observed *in vivo*, and NA variants generated by *in vitro* passage of the virus in the presence of zanamivir or GS4071 have been shown to be significantly less infectious than wild type virus. The most common mutation, an alteration in Glu119 at the NA active site, is associated with resistance to zanamivir but not to GS4071.

Clinical trials of oseltamivir are ongoing, and preliminary data on the compound are promising especially with regard to adverse effects. ▲