

Antiviral Efficacy of Peramivir (BCX-1812) against Highly Pathogenic Avian Influenza Viruses (H5N1) with or without the H274Y mutation in mouse

Shionogi: Makoto Kodama, Masanori Kobayashi, Takeshi Noshi, Ryu Yoshida, Akihiko Sato

Hokkaido University: Naoki Nomura, Kosuke Soda, Masatoshi Okamatsu, Yoshihiro Sakoda, Hiroshi Kida

Background: Peramivir is a potent influenza virus neuraminidase (NA) inhibitor. A single intravenous injection of peramivir was shown to be effective in clinical studies, leading to marketing authorization in January 2010 in Japan (Rapiacta®). In this study, we evaluated the efficacy of peramivir against highly pathogenic A/Hong Kong/483/97 (HK483) influenza viruses in a mouse model.

Methods: Viruses were generated from plasmids containing the full-length cDNA of HK483 influenza viruses. Mutations encoding substitutions at conserved NA residues (H274Y) were separately introduced into the NA plasmids by site-directed mutagenesis (HK483/H274Y). Recombinant viruses were produced in embryonated chicken eggs and inoculated to BALB/c mice (10MLD₅₀). Treatment with antiviral compound was started immediately after virus inoculation. Peramivir was administered intravenously injection by single or once daily for 5 days, and oseltamivir phosphate was administered orally twice daily for 5 days. Antiviral efficacy was determined by the prevention of death at 14 days and by the virus reduction in lung or brain at designated dates after virus inoculation.

Results: Single treatment with peramivir (30 mg/kg) significantly prevented death (100% survived) of mice inoculated with lethal doses of HK483 virus and reduced viral titer in lung and brain. Moreover, peramivir at multi-dosing at 30 mg/kg (once daily for 5 days) significantly prevented the death of mice inoculated with lethal doses of HK483/H274Y (70% survived) compared to untreated control (100% mortality). Conversely, survival rate by multi-dosing of oseltamivir phosphate at 30mg/kg (twice daily for 5 days) was 67% and 20% after lethal doses of HK483 and HK483/H274Y, respectively.

Conclusions: These data demonstrate that peramivir has a strong inhibitory activity against highly pathogenic avian influenza viruses with or without the H274Y mutation. Notably, peramivir showed this therapeutic effect against HK483/H274Y with applicable dosing in human.