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One-day oral dosing of S-033188, a novel inhibitor of influenza virus Cap-dependent endonuclease, exhibited significant reduction of viral titre and prolonged survival in mice infected with influenza B virus

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Background: Both epidemic and pandemic influenza are major public health concerns, but currently, no antiviral drug has been shown to definitively reduce serious complications, hospitalization, or mortality in a randomized clinical trial. Both influenza A and B viruses are responsible for seasonal influenza. Therefore, novel anti-influenza drugs should ideally have activity against both A and B influenza viruses. S-033188 is an orally available small molecule inhibitor of cap-dependent endonuclease that is essential for transcription and replication of influenza A and B virus. We previously demonstrated effectiveness of S-033188 against influenza A virus in nonclinical phamacorogy models. In this study, we evaluated the efficacy of 1 day oral dosing of S-033188 in mice infected with influenza B virus.

Material/methods: Female BALB/c mice were intranasally inoculated with B/Hong Kong/5/72 strain (mouse-adapted) at 1.98×10^6 tissue culture infectious dose 50 ($TCID_{50}$)/mouse. Immediately after infection, mice were orally treated with S-033188 (0.5, 5, or 50 mg/kg) or vehicle (0.5 w/v% methylcellulose) twice a day for 1 day, or oseltamivir phosphate (5 or 50 mg/kg) twice a day for 5 days. Viral titer in the lung 1 day after the infection was determined. Survival time and body weight change were then monitored through a 14-day period after infection. Mice were euthanized and regarded as dead if their body weights were lower than 70% of the initial body weights according to humane endpoints.

Results: S-033188 (5 or 50 mg/kg, BID for 1 day) completely eliminated mortality in mice infected with influenza B virus, whereas in mice treated with clinically equivalent dose of oseltamivir phosphate (5 mg/kg, bid for 5 days) only 20% of animals survived (Fig.1). S-033188 treatment also significantly reduced viral titer and prevented body weight loss, consistent with the prolonged survival.

Conclusions: One day oral dosing of S-033188 (5 or 50 mg/kg BID) exhibited significant efficacy in mice infected with influenza B virus compared to clinically equivalent dosing of oseltamivir phosphate.

Fig.1 Protective effect of S-033188 on mortality in mice infection with B/Hong Kong/5/72 strain