Therapeutic Effect of Delayed Treatment with a Second Generation 3CL Protease Inhibitor S-892216 in Hamsters Infected with SARS-CoV-2

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Background and Purpose

SARS-CoV-2 and COVID-19 remain a major global health challenge. We have discovered a second-generation small molecule 3CL protease inhibitor S-892216 that is proceeding with phase 1 study in Japan. S-892216 has potent antiviral activity and addresses current treatment concerns of currently available antivirals regarding drug-drug interaction (DDI) and safety. We evaluated the therapeutic effect of S-892216 by using SARS-CoV-2 infected hamster model. In this study, virus titer in lungs and nasal turbinates (NT), lung inflammation, body weight loss and lung weight increase caused by SARS-CoV-2 infection were analyzed.

Methods

Syrian hamsters were intranasally inoculated with hCoV-19/Japan/TY41-702/2022 (SARS-CoV-2 Omicron BE.1/BA.5-like). The hamsters were orally treated twice daily with S-892216 0.1, 1, and 10 mg/kg or ensitrelvir 50 mg/kg, or subcutaneously treated with nirmatrelvir 750/250 mg/kg (750 mg/kg for the loading dose and 250 mg/kg for the maintenance doses) from 1 day post infection for 5 days (1). Lungs and NT were collected for virus titers and lung inflammation evaluation. Lung weights were measured 7 days post infection and body weight changes were monitored until 10- or 14-days post infection.

Results

Figure 1-1 Effect of 24 hr-delayed treatment with S-892216 or nirmatrelvir on lung and NT virus titer, and lung inflammation of hamster infected with SARS-CoV-2 Omicron strain.

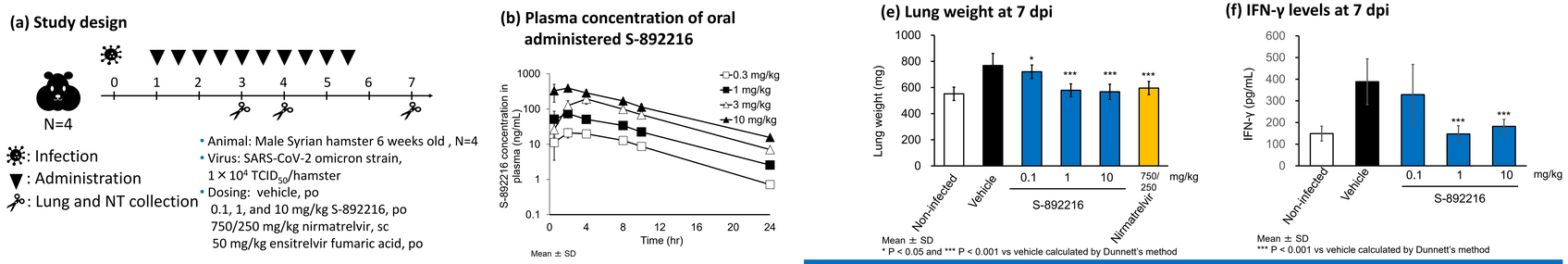


Figure 1-2 Effect of 24 hr-delayed treatment with S-892216 or ensitrelvir on lung and NT virus titer of hamster infected with SARS-CoV-2 Omicron strain.

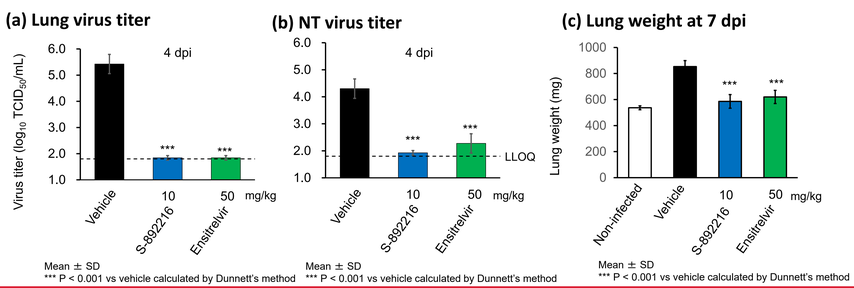
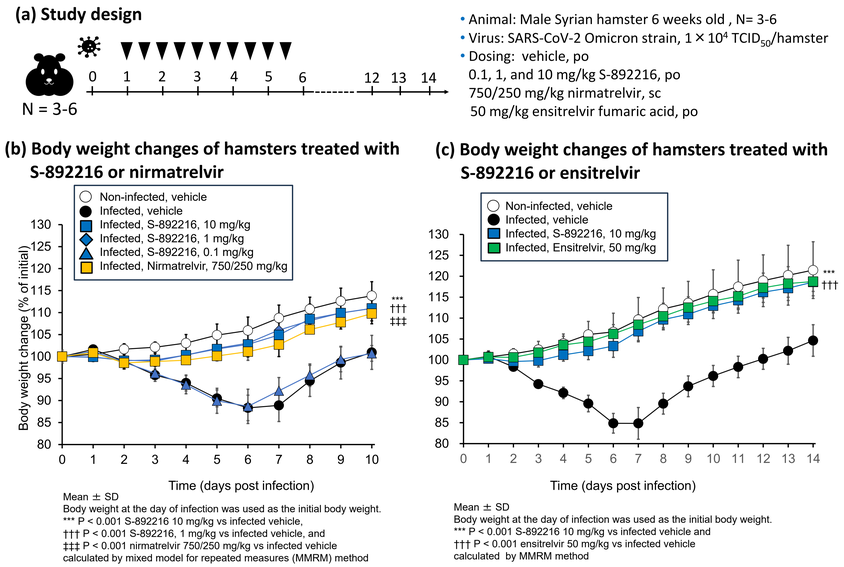


Figure 2 Effect of 24 hr-delayed treatment with S-892216, nirmatrelvir, or ensitrelvir on body weight losses of hamster infected with SARS-CoV-2 omicron strain.



Conclusion

Oral treatment with S-892216 exhibited therapeutic effect in SARS-CoV-2 infected hamsters. Furthermore, S-892216 showed comparable efficacy at lower dosages compared to nirmatrelvir and ensitrelvir. These findings suggest that S-892216 could be used at lower dosage than the current treatment options in clinical settings, potentially minimizing drug-drug interactions. We will evaluate DDI and the safety potential of S-892216 in clinical trials in the future.

Acknowledgement

SARS-CoV-2 strains were kindly gifts from National Institute of Infectious Diseases (NIID). This work was supported by the Japan Agency for Medical Research and Development (AMED) under Grant Numbers JP21fk0108584 and JP22fk0108522.

Reference

(1) Kuroda T et al. *J Antimicrob Chemother.* 2023 Apr 3;78(4):946-952

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