Sotrovimab Lacks Efficacy in Treatment of Syrian Golden Hamsters Infected With SARS-CoV-2 BQ.1.1

672

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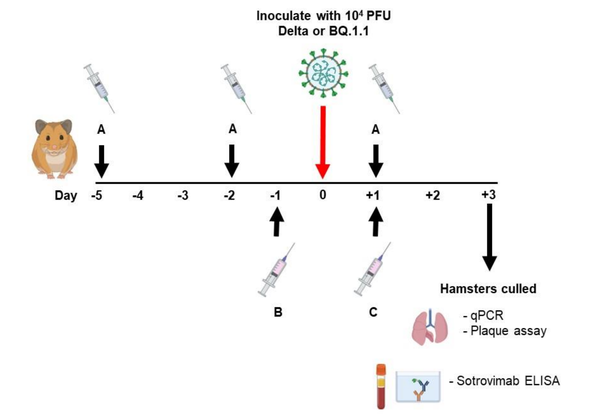
BACKGROUND

- Sotrovimab (SOT) demonstrates molar potency against previous SARS-CoV-2 variants, reducing the risk of hospitalization and death in patients at high risk of progression to severe COVID-19[1].
- With the emergence of Omicron sub-lineages all mAbs have lost varying degrees of neutralization capacity and previously approved mAbs are no longer recommended by the WHO[2,3].
- The continued use of SOT is not supported by current PK-PD understanding of neutralisation. However, published preclinical studies indicate virological efficacy in prophylaxis for BQ.1.1[4,5].
- This study investigated the efficacy of SOT in healthy and immunocompromised hamsters infected with Delta or BQ.1.1 variants using models reflective of prophylaxis and treatment.

METHODS

- Male Syrian Golden Hamsters (80-100g) were randomly assigned into groups and a subset was immunosuppressed using IP-administered cyclophosphamide (Fig. 1).



(A) Subset of hamsters immunosuppressed using IP-injected cyclophosphamide (100 mg/kg)
(B) Intramuscular SOT (14 mg/kg) administered 24 h before inoculation (prophylaxis groups)
(C) Intramuscular SOT (14 mg/kg) or vehicle control administered 24 h after inoculation (treatment groups)

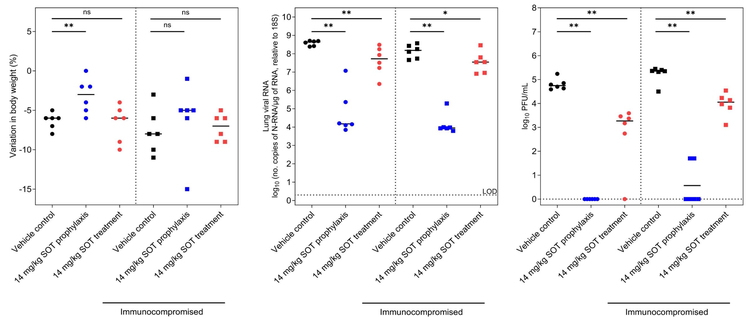
Figure 1. *Diagrammatic representation of the experimental design employed.*

- Hamsters were administered SOT (14 mg/kg) or equal volumes of saline intramuscularly 24 h before or after inoculation.
- Hamsters were intranasally inoculated with 10^4 PFU of SARS-CoV-2 Delta (B.1.617.2) or Omicron (BQ.1.1).
- At 3-dpi all hamsters were sacrificed, the lung was collected, and viral replication was quantified using qPCR and plaque assay.
- Terminal plasma samples were isolated for the quantitative detection of SOT using ELISA.
- Unpaired Mann-Whitney tests were applied to determine the significance between SOT-administered groups and controls.

Sotrovimab lacks virological efficacy against SARS-CoV-2 BQ.1.1 using a model reflective of treatment in hamsters.

RESULTS

(a.) SARS-CoV-2 Delta (B.1.617.2)



(b.) SARS-CoV-2 Omicron (BQ.1.1)

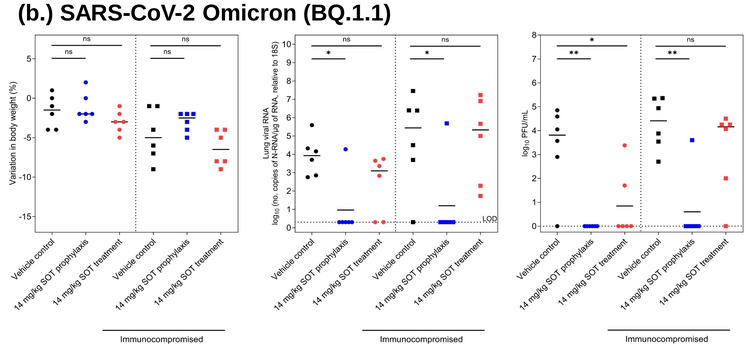


Figure 2. *Virological efficacy of SOT in healthy and immunocompromised Syrian Golden Hamsters infected with (a.) SARS-CoV-2 Delta (B.1.617.2) or (b.) SARS-CoV-2 Omicron (BQ.1.1) utilizing experimental designs reflective of prophylaxis and treatment.*
(left) Variation in hamster weight compared to -1-dpi, (middle) lung viral RNA, and (right) replicating lung viral titres at 3-dpi.
Horizontal bar represents the median value. Statistical significance, P<0.05. ns, not significant. LOD, limit of detection.

- At 3-dpi greater weight reductions were observed for the BQ.1.1-inoculated animals compared to Delta, relative to controls, across all SOT-administered groups (Fig. 2).
- qPCR data (Fig. 2 & Table 1.) revealed statistically significant log_{10}-fold reductions in pulmonary viral RNA in prophylaxis and treatment for Delta but only in prophylaxis for BQ.1.1-inoculated hamsters, relative to controls.
- Lung plaque data (Fig. 2) revealed a statistically significant reduction in viral titres for the SOT-treated, Delta-inoculated, hamsters (1.32, P=0.001) but not for BQ.1.1-inoculated (1.35, P=0.186), relative to controls, in the immunocompromised groups.
- Hamster SOT plasma concentrations were comparable across Delta- and BQ.1.1-inoculated groups at 3-dpi: 44.13 ± 5.40, 47.06 ± 4.44 µg/mL, respectively, and were consistent with previous hamster studies[4].

RESULTS

Table 1. *Mean log_{10} fold-changes in SARS-CoV-2 N-RNA, relative to vehicle control groups, in hamster lung samples at 3-dpi following inoculation with 10^4 PFU Delta or BQ.1.1 variants.*

	Log_{10} fold-change in pulmonary viral RNA compared to vehicle control			
SARS-CoV-2 variant	14 mg/kg SOT dosed 24h before inoculation		14 mg/kg SOT dosed 24h after inoculation	
	Healthy	Immunocompromised	Healthy	Immunocompromised
Delta	-3.65, P=0.001	-2.29, P=0.001	-0.38, P=0.004	-0.58, P=0.046
BQ.1.1	-1.36, P=0.011	-1.83, P=0.021	-0.52, P=0.063	-0.11, P=0.500

CONCLUSIONS

- Previous preclinical studies have shown virological efficacy of SOT against BQ.1.1 in experimental designs reflective of prophylaxis for hamster[4] and non-human primate[5].
- Here, we demonstrate a lack of virological efficacy of SOT against BQ.1.1 in immunocompromised hamsters using an experimental design reflective of treatment.
- Virological efficacy was confirmed against the Delta variant in prophylaxis and treatment designs.
- These findings are consistent with SOT neutralisation PK-PD understanding from RCTs[3] and observational studies for at-risk COVID-19 patients[6].
- Interestingly, SOT did not block infection of Delta or BQ.1.1 when given in prophylaxis.
- The relevance of changes in viral RNA at high SOT concentrations, early in the profile, to longer-term prophylaxis is unclear and warrants further investigation.
- Caution should be taken when interpreting preclinical experimental designs that may not be reflective of the clinical use case.

ADDITIONAL INFORMATION

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