In vivo activity of Sotrovimab against BQ.1.1 Omicron sublineage

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Abstract

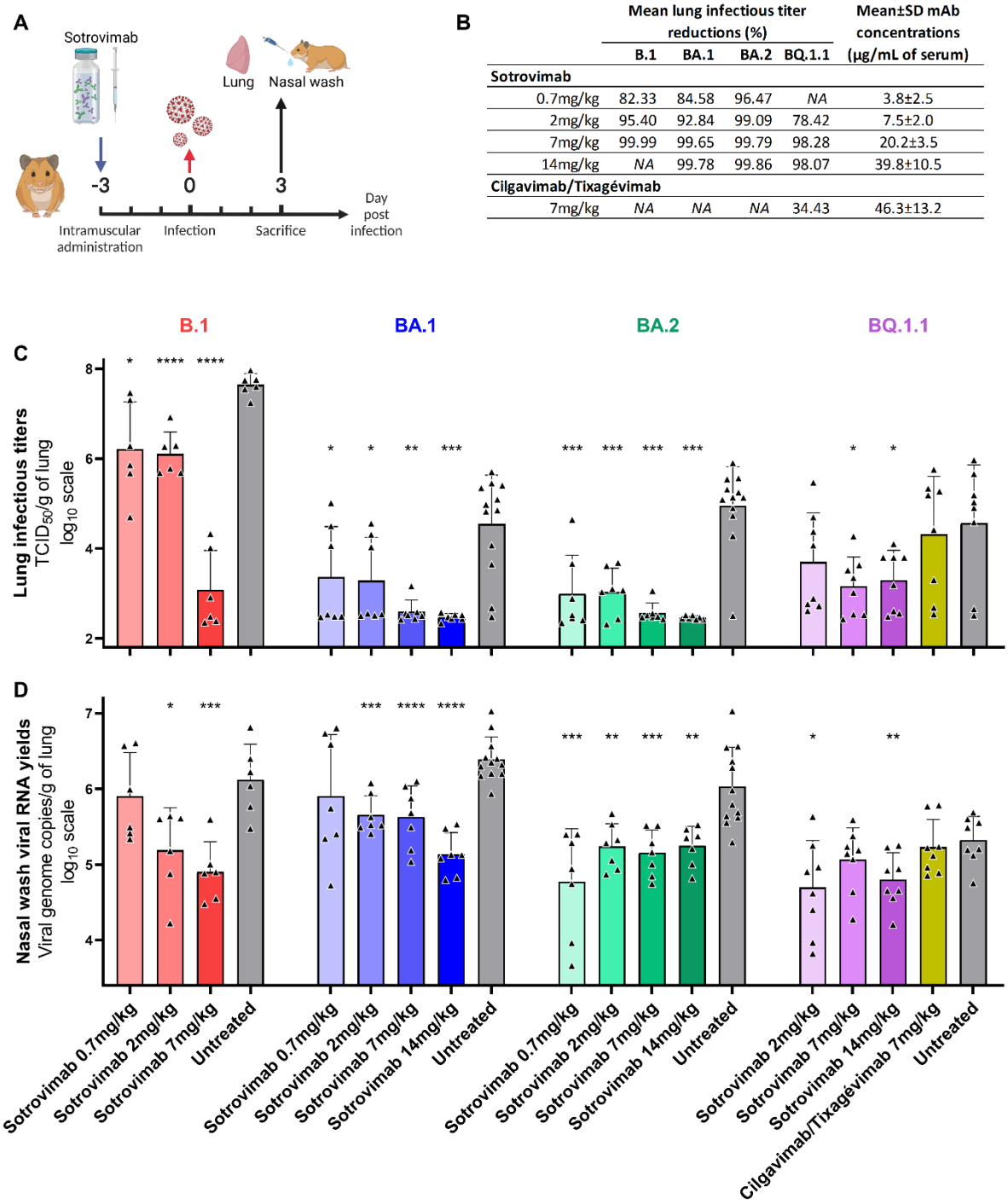
The successive emergence of SARS-CoV-2 Omicron variants has completely changed the modalities of use of therapeutic monoclonal antibodies. Recent in vitro studies indicated that only Sotrovimab has maintained partial activity against BQ.1.1, a sub-variant of BA.5 that is spreading in the USA and Europe. In the present study, we used the hamster model to determine whether Sotrovimab retains antiviral activity against BQ.1.1 in vivo. Our results show that at exposures consistent with those observed in humans, Sotrovimab remains active against BQ.1.1 variant, although at a lower level than that observed against the first globally dominant BA.1 and BA.2 Omicron sublineages.

Main text:

Therapeutic monoclonal antibodies (mAbs) targeting the SARS-CoV-2 spike protein have been widely used during the current COVID-19 pandemic, particularly in immunocompromised patients in whom vaccination induces an inadequate immune response. However, almost all clinically approved mAbs have lost part or all of their neutralizing activity against the different sub-lineages of the Omicron variant that have successively spread globally and contain several mutations in the spike protein associated with potential escape from humoral immunity and higher transmissibility[1-3]. While Bebtelovimav, Cilgavimab, Imdevimab and Sotrovimab retained some activity against BA.5, only Sotrovimab maintains partial activity against BQ.1.1, a BA.5 subvariant with increasing incidence in the USA and Europe[4-7]. It has been shown that despite its loss of in vitro neutralising activity against BA.2 and BA.5, Sotrovimab exhibits antiviral activity in Syrian hamsters against these Omicron variants[8,9]. It is therefore urgent to determine whether this Mab retains activity in vivo against BQ.1.1 at exposures similar to those observed in humans.

In this study, the efficacy of Sotrovimab against three clinical strains of Omicron variant (BA.1, BA.2 and BQ.1.1) was assessed in a hamster model using an ancestral B.1 strain as reference. Three days before the intranasal infection, groups of animals received pre-exposure prophylaxis by intramuscular injection of increasing doses of Sotrovimab and were compared with untreated animals receiving an isotype control mAb (Palivizumab)(**Fig 1A**). Overall, results showed that Sotrovimab exhibited an antiviral activity against all viruses, although less marked for BQ.1.1, in agreement with recently published in vitro data based on a VeroE6/TMPRSS2 cell assay with replicating virus[7]. Indeed, administration of Sotrovimab always dose-dependently reduced infectious titers in lungs. When compared with corresponding untreated animals, mean reductions ranged between 82.33 and 99.99% for the ancestral strain, between 84.58 and 99.78% for BA.1, between 96.47 and 99.86% for BA.2 and between 78.42% and 98.28% for BQ.1.1 (**Fig 1B-C**). This decrease was significant for all doses of Sotrovimab used against all viruses (*p* values ranging between <0.0001 and 0.0369), except with the dose of 2mg/kg for the BQ.1.1. Furthermore, administration of Sotrovimab led to a reduction of viral RNA yields in nasal washes for all doses with all viruses (*p* ranged between <0.0001 and 0.0227), except with the dose of 0.7mg/kg for the ancestral strain and the BA.1 variant, and the dose of 7mg/kg for the BQ.1.1 (**Fig 1D**). Mean serum concentrations of Sotrovimab at 3dpi were measured and ranged between 3.8 and 39.8µg/mL (Fig 1B and S1). Pharmacokinetic data published by the US Food Drug Administration in humans indicate that mean serum concentrations peak at 143µg/mL and remain above 40µg/mL twenty-nine days after intravenous administration of 500mg Sotrovimab (COMET-ICE trial (NCT04545060)). These exposures are higher than those measured in groups of animal in which antiviral activity against the BQ1.1 variant is obtained, suggesting that Sotrovimab may retain some activity against this variant in treated patients. Finally, a group of animal was also treated with 7mg/kg of Cilgavimab/Tixagévimab and infected with BQ.1.1. No antiviral activity was obtained at this dose, in accordance with in vitro data published recently, and despite mean serum mAb concentrations above the geometric mean of 37.2µ/mL observed twenty-nine days after the administration of 600mg of this mAb cocktail during the TACKLE trial (NCT04723394).

Our data demonstrate that Sotrovimab retains some antiviral activity in vivo against the BQ.1.1 variant, although at a lower level than that observed against the first globally dominant Omicron sublineages, in agreement with recently published in vitro data[7]. While comparison of exposure data in animals with those observed in humans suggests potential efficacy in treated patients, the clinical impact of Sotrovimab treatment will need to be documented in more relevant models such as non-human primates and in humans. The constant antigenic evolution of SARS-CoV-2 reinforces the need for therapeutic antibodies and antiviral molecules with broad-spectrum activity and that may be used alone or in combination.



	Mean lung infectious titer reductions (%)				Mean±SD mAb concentrations (µg/mL of serum)
	B.1	BA.1	BA.2	BQ.1.1	
Sotrovimab					
0.7mg/kg	82.33	84.58	96.47	*NA*	3.8±2.5
2mg/kg	95.40	92.84	99.09	78.42	7.5±2.0
7mg/kg	99.99	99.65	99.79	98.28	20.2±3.5
14mg/kg	*NA*	99.78	99.86	98.07	39.8±10.5
Cilgavimab/Tixagévimab					
7mg/kg	*NA*	*NA*	*NA*	34.43	46.3±13.2

Figure 1: In vivo efficacy of Sotrovimab and Cilgavimab/Tixagévimab against BA.1, BA.2 and BQ.1.1 Omicron variants.

(**A**) Experimental timeline. (**B**) Mean lung reduction infectious titer reduction compared to untreated animals and mean serum concentrations of mAbs at 3 dpi. (**C**) Lung infectious titers and (**D**) viral RNA yields in nasal washes at 3 dpi (Data represent mean ± SD of individual data). ****, ***, ** and * symbols indicate that the average value for the group is significantly lower than that of the untreated group with a p-value < 0.0001, ranging between 0.0001–0.001, 0.001–0.01, and 0.01–0.05, respectively.

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Author contribution

Conceptualisation: JSD, XDL, AN
Data curation, formal analysis, investigation: JSD, OB, FT, AN
Funding acquisition, supervision: XDL, AN
Validation, writing – original draft: JSD, AN
Writing – review & editing: OB, FT, XDL

Disclosure of financial associations and conflicts of interest

The authors declare that there is no conflict of interest or financial association.

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