In vitro activity of therapeutic antibodies against SARS-CoV-2 Omicron BA.1 and BA.2

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Article

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Abstract

The replacement of the Omicron BA.1 variant of SARS-CoV-2 by the BA.2 sub lineage, which has a different set of mutations in the spike glycoprotein, alters the spectrum of activity of therapeutic antibodies. In this study, we compared the neutralising power of monoclonal antibodies against the Omicron BA.1 and BA.2 variants, with an ancestral strain (D614G) and a Delta variant as reference. Sotrovimab is less active against BA.2 than against BA.1 (fold change reduction ~1,5). Within the Evusheld/ AZD744 cocktail, Cilgavimab is more active against BA.2 than against BA.1 (fold change increase ~32), whilst activity of Tixagevimab remains very low. In total, the activity of Evusheld is significantly improved (fold change increase ~10 compared to BA.1).

Main

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China in late 2019 and then spread rapidly, causing the first pandemic of the 21st century. Since then, epidemic spread has been sustained by the continued emergence of new variants that combine increased transmissibility[1] and antigenic shift[2,.] We are currently witnessing the replacement of the Omicron BA.1 variant by a new sub lineage, BA.2, which also emerged in South Africa in late 2021. Omicron BA.2 has fewer mutations than BA.1 in the spike glycoprotein, some of which are shared with BA.1 and others are original. This new mutation pattern has the potential to alter the activity of therapeutic monoclonal antibodies currently in clinical use against Omicron BA.1.

In the current study, we tested the neutralising activity of therapeutic antibodies against clinical strains of the BA.1 and BA.2 sub lineages of the B.1.1.529 Omicron variant, using the BavPat1 European ancestral strain (lineage B.1, D614G) and a Delta variant (B.1.617.2) as reference. We tested therapeutic antibodies currently in use that have been shown to retain neutralising activity against BA.1[3]. All target the spike Receptor Binding Domain (RBD)[4,5] (Cilgavimab/AZD1061 and Tixagevimab/AZD8895, part of the Evusheld/AZD7442 cocktail) and more precisely the core region[4] for Sotrovimab/Vir-7831.

We used a standardised methodology for the evaluation of antiviral compounds based on the reduction of RNA yield[6], which has been applied to SARS-CoV-2[3,7]. The assay was performed in VeroE6 TMPRSS2 cells and the amount of viral RNA in the supernatant medium was quantified by qRT-PCR 48h post-infection to determine the 50% effective concentration (EC_{50}).

Table 1: Activity of therapeutic antibodies against B.1, Delta and Omicron BA.1, BA.2 variants. Interpolated EC_{50} values are expressed in ng/mL. For BA.1 and BA.2 strains, the EC_{50} is the mean of two independent experiment (n=2), each including three replicates. (n.n: non-neutralising). MNU_{50}: neutralizing capacity per treatment expressed in million units. One unit is defined as the amount of a given antibody needed to provide 50% neutralization of 100 TCID50 of a given strain. Doses refer to treatments authorized in the European Union

(Sotrovimab: 500 mg IV [8]; AZD7442: 300 mg IM (Cilgavimab 150 mg + Tixagevimab 150 mg). Fold change reduction were calculated in comparison with the ancestral B.1 strain.

Antibody			Strain			
			BavPat B.1	Delta	BA.1	BA.2
GSK/ Vir	Sotrovimab (vir-7831)	EC_{50}	55,2	51,5	294,8	441,0
		MNU_{50}	60,4	64,7	11,3	7,6
		fold-change	-	0,9	5,3	8,0
AstraZeneca	Cilgavimab (AZD1061)	EC_{50}	32,8	40,3	1617,0	49,8
		MNU_{50}	30,5	24,8	0,6	20,1
		fold-change	-	1,2	49,2	1,5
	Tixagevimab (AZD8895)	EC_{50}	18,3	17,2	n.n	n.n
		MNU_{50}	54,7	58,1	n.n	n.n
		fold-change	-	0,9	-	-
	Evusheld (AZD7442)	EC_{50}	27,0	24,7	712,2	73,3
		MNU_{50}	74,0	80,8	2,8	27,3
		fold-change	-	0,9	26,3	2,7

Our results support previous studies reporting that Sotrovimab retains some neutralising activity against the BA.1 sub lineage *in vitro*[2,3,9,10]. In the case of the BA.2 variant (Table 1, supplemental Fig.1), with an EC_{50} increasing from 55.2 (B.1) to 441(BA.2) ng/mL, we observe a decrease in neutralisation activity by a factor of ~8 (Table 1) compared to the ancestral B.1 strain, and ~1.5 compared to BA.1. This result is consistent with data from Vir Biotechnology using a pseudotype virus harboring all Omicron BA.2 spike mutations[11].

The neutralising activity of Tixagevimab is very low against both BA.1 and BA.2 (EC_{50} >5000 ng/L, see Table 1). In contrast, Cilgavimab regains neutralizing power against BA.2 with an EC_{50} increasing only from 32.8 (B.1) to 49.8 ng/mL (BA.2), which represents a very limited loss of neutralising activity (B.1/BA.2 ratio: ~1.5, Table 1). In comparison, a 49-fold B.1/BA.1 reduction in neutralisation activity was observed with this monoclonal antibody. In short, this indicates that Cilgavimab exhibited 32-fold greater activity against BA.2 compared to BA.1 in our assays. This could be due to the absence in the BA.2 RBD of the G446S mutation, which is located in a region identified as critical for Cilgavimab neutralising activity[4]. When Cilgavimab was tested in combination with Tixagevimab, as proposed in the Evusheld therapeutic cocktail[12], the EC_{50} shifted from 27 (B.1) to 73.3 ng/mL (BA.2), *i.e.* a 2.7-fold decrease in neutralisation activity when comparing BA.2 with B.1, but a 10-fold increase when comparing BA.2 with BA.1 (Table 1). This is in line with results recently produced using spike protein-pseudotyped lentiviruses[13,14].

The analysis of our results should be done in the context of the actual treatments administered to patients at risk of developing severe forms of Covid-19. Sotrovimab is registered in the European Union

for the early treatment of infections with a single intravenous injection of 500 mg and the AZD7442 cocktail for the prophylaxis of infection with a single 300 mg dose (150 mg Tixagevimab + 150 mg Cilgavimab, IM administration) but a possibility of double-dose curative use (300 mg Tixagevimab + 300 mg Cilgavimab, IV injection) was left open. As previously described[3], based on the EC_{50} values, we calculated the neutralizing capacity of each treatment expressed as MNU_{50} (Table 1). This allows a realistic comparison between treatments of the neutralization capacity against each variants.

For AZD7442, the restoration of Cilgavimab activity against BA.2 results in a significantly improved activity per treatment compared to BA.1 (27.3 MNU_{50} *vs* 2.8 MNU_{50}). When the activity of a 300 mg dose of AZD7442 is compared to that of a 500 mg dose of Sotrovimab, the advantage goes to Sotrovimab for the BA.1 variant (11.3 MNU_{50} *vs* 2.8 MNU_{50} for AZD7442), but to AZD7442 for the BA.2 variant (27.3 MNU_{50} *vs* 7.6 MNU_{50} for Sotrovimab). The latter result was due to a combination of increased activity of AZD7442 against BA.2, but also slightly lower activity of Sotrovimab against BA.2 compared to BA.1 (7.6 *vs* 11.3 MNU_{50}).

We conclude that against BA.2 and compared to BA.1, Sotrovimab 500 mg retains neutralising activity despite a further modest decrease in its activity which should be closely monitored to ensure that the dose of 500 mg is sufficient to provide a therapeutic benefit against Omicron BA.2. The activity of a 300 mg dose of AZD7442 against BA.1 is limited *in vitro* and *in vivo* [15], leading to a recent FDA recommendation to use a 600 mg dose instead[16]. The restored activity of Cilgavimab against BA.2 allows AZD7442 to regain significant activity against this variant. If a dose of 600 mg becomes the norm, the expected activity against BA.2 would be in the order of 55 MNU_{50}, which is close to the activity originally observed with a 300 mg treatment against the European B.1 variant (~74 MNU_{50}). However, as the neutralising activity of Tixagevimab is not restored against BA.2, it remains to be assessed by *in vivo* experiments whether the combination of Cilgavimab and Tixagevimab is still relevant compared to Cilgavimab alone, and to what extent AZD7442 acts against BA.2 as a monotherapy or a combination of antibodies.

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