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Letter to the Editor

Impact of SARS-CoV-2 omicron BA.1 and delta AY.4.2 variants on the neutralization by sera of patients treated with different authorized monoclonal antibodies

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To the Editor,

Among the different SARS-CoV-2 variants of concern [1], Delta and Omicron currently account for the vast majority of cases worldwide, with the latter rapidly replacing the former in many countries [2]. Notably, Omicron is the most divergent from the wild-type B.1 strain, with 15 amino acid changes in the receptor-binding domain of the spike protein, the major target of neutralizing antibodies. Indeed, Omicron partly escapes natural or vaccine-elicited immunity [3] and can decrease the efficacy of currently licensed therapeutic monoclonal antibodies (mAbs) [4,5].

We assessed the *ex vivo* inhibition of Omicron and Delta variants by sera obtained from unvaccinated patients treated with one of the three licensed mAb preparations, namely bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab. A pair of patient sera samples was collected, the first before (to exclude any prior neutralizing antibody (NtAb) activity) and the second 1 hour after mAbs infusion.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (Neutro-COVID observational study, protocol number 4069/21). Written informed consent was obtained from all the patients enrolled.

The efficacy of the mAbs was assessed by a live virus neutralization assay against wild type (GISAID accession number EPI_ISL_2472896), Delta (EPI_ISL_2840619), the Omicron sublineage BA.1 (EPI_ISL_6777160), and the Delta sublineage AY.4.2 (EPI_ISL_6943992), recently detected in Italy [6] and carrying the additional Y145H and A222V spike substitutions (details of each viral stock are indicated in Table S1). NtAb titres were determined by a microneutralization live virus assay [7] and defined as the reciprocal value of the sample dilution that showed a 50% protection of virus-induced cytopathic effect (ID_{50}).

Statistical analyses were performed using IBM SPSS Statistics, version 20. Sera with $ID_{50} < 10$ were defined as negative and scored as 5 for statistical analysis. Data were expressed as median (IQR), as appropriate for the distribution of data based on the Shapiro-Wilk test for normality. The Kruskal-Wallis test followed by Mann-Whitney test post hoc analysis was used to compare independent groups, and the Friedman test followed by Wilcoxon rank sum test post hoc analysis was used to compare multiple paired data. Spearman analysis was used to measure the correlation between NtAb titres against the different variants.

Of 30 patients studied (14 males, age 59 ± 18 years, full characteristics summarized in Table S2), one was asymptomatic and the others had mild symptoms such as cough ($n = 19$), fever ($n = 17$), headache ($n = 13$), gastrointestinal symptoms ($n = 4$), and dyspnoea ($n = 2$). Patients were randomly treated with bamlanivimab/etesevimab ($n = 10$), casirivimab/imdevimab

The omicron variant discussed in this study is the omicron BA.1 to distinguish it from other omicron variants emerging later including BA.1.1, BA.2 and BA.3.

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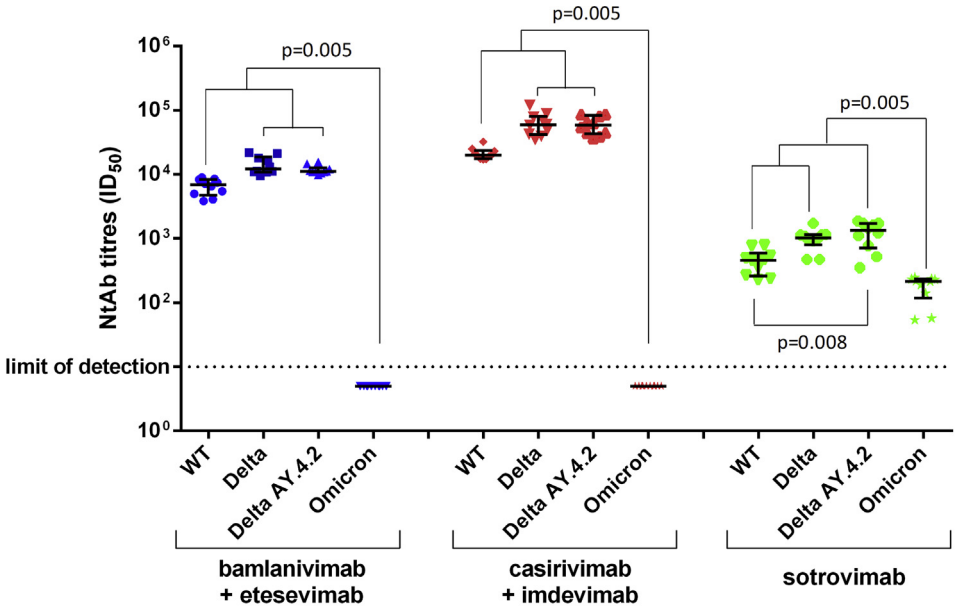

	bamlanivimab + etesevimab	casirivimab + imdevimab	sotrovimab
WT	6,792 (4,736-8,328)	19,814 (17,459-23,471)	456 (259-592)
Delta	12,145 (10,840-18,667)	58,858 (41,585-79,971)	1,023 (798-1,134)
Delta AY.4.2	11,067 (10,757-12,614)	58,602 (42,941-82,960)	1,333 (708-1,714)
Omicron	<10	<10	216 (118-233)

Fig. 1. *Ex vivo* anti–SARS-CoV-2 wild type, Delta, Delta AY.4.2, and Omicron neutralizing antibody (NtAb) titres measured in sera from 30 patients after infusion of the bamlanivimab/etesevimab (in blue), orcasirivimab/imdevimab (in red), or sotrovimab (in green) monoclonal antibody cocktails. Paired data were analyzed by the nonparametric Wilcoxon signed rank sum test. NtAb titre before infusion was negative against each variant tested (data not shown in figure). Median ID_{50} (IQR) are indicated in the table below the figure. ID_{50}, the reciprocal value of the sera dilution showing the 50% protection of virus-induced cytopathic effect; NtAb, neutralizing antibody.

(n = 10), or sotrovimab (n = 10), 3.5 ± 1.7 days from diagnosis. None of the patients required hospitalization. All preinfusion sera were negative for SARS-CoV-2 NtAb activity. In postinfusion sera, casirivimab/imdevimab, bamlanivimab/etesevimab, and sotrovimab showed activity against the wild-type variant (19,814 (17,459–23,471), 6792 (4736–8328), and 456 (259–592)), the Delta variant (58,858 (41,585–79,971), 12,145 (10,840–18,667), and 1023 (798–1134)), and Delta AY.4.2 (58,602 (42,941–82, 960), 11,067 (10,757–12,614), and 1333 (708–1714)). Notably, sotrovimab was the only active treatment against the Omicron variant (216 (118–233)) (Fig. 1).

Within each individual treatment group, the NtAb titres to Delta and Delta AY.4.2 variants were significantly higher than those to wild type (p = 0.008 for AY.4.2 vs. wild type with sotrovimab; p = 0.005 for all other comparisons). NtAb titres to wild type, Delta, and Delta AY.4.2 variants were higher than those to Omicron within all individual treatment groups (p = 0.005 for all comparisons).

Comparing treatments, casirivimab/imdevimab neutralizing titres were significantly higher than bamlanivimab/etesevimab and sotrovimab against wild type, Delta, and the Delta AY.4.2 variants, and bamlanivimab/etesevimab neutralizing titres were significantly higher than sotrovimab for the same variants (p < 0.001 for all comparisons). When considering all 30 postinfusion sera, a significant correlation was observed between NtAb titres to any pair of wild type, Delta, and Delta AY.4.2 variants (p < 0.001 for all comparisons), whereas NtAb titres to Omicron correlated significantly only to NtAb titres to wild-type virus (p = 0.009) (Fig. S1).

A previous report documented *in vitro* inhibition of the Delta variant by the individual mAbs etesevimab, casirivimab, and imdevimab, but not bamlanivimab, at slightly higher levels compared with the wild-type B.1 virus [8]. Our study confirms these findings by testing the bamlanivimab/etesevimab and casirivimab/imdevimab cocktails in an *ex vivo* format. In addition, we demonstrated maintenance of activity against Delta AY.4.2 for the first time, implying that the additional Y145H and A222V mutations have no impact on neutralization by these mAbs preparations. Most importantly, our results support full escape of commonly used mAbs cocktails by the Omicron variant, as recently reported [4], although sotrovimab appears to retain activity against all variants tested, including Omicron (albeit reduced by an average 2.7-fold in paired measurements), similar to what has been reported in the literature [5,9]. Since Omicron has rapidly replaced the circulating variants, the mAbs arsenal should be updated accordingly. Clearly, surveillance of SARS-CoV-2 evolution over time and in different geographical areas remains a priority to adapt our defences against the pandemic.

Transparency declaration

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Author contributions

IV, MZ, DF, and MRG conceived the idea for this work. FD, LF, VM, AL, and ES performed the experiments. FD, LF, BR, and IV

contributed to the data analysis. VM, AL, ES, GZ, MRG, BR, and DF collected the samples and provided the virus lineages for this work. IV, FD, and MZ wrote the paper. All authors contributed to the revision and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.03.005.

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