Impact of SARS-CoV-2 omicron and delta sub-lineage AY.4.2 variant on neutralization by sera of patients treated with different licensed monoclonal antibodies

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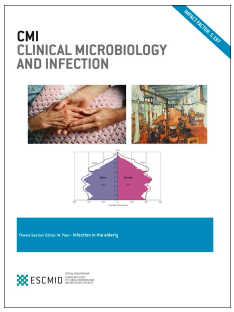

Impact of SARS-CoV-2 omicron and delta sub-lineage AY.4.2 variant on neutralization by sera of patients treated with different licensed monoclonal antibodies

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Category: Letter

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To the Editor,

Among the different SARS-CoV-2 variants of concern (VOCs) [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 was collected, the first before (to exclude any prior NtAb activity) and the second one hour post 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 by 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), omicron (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 Supplementary table S1). Neutralizing antibody (NtAb) titers 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, while 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 titers against the different variants.

Of 30 patients studied (14 males, 59±18 years, full characteristics summarized in supplementary table S2), one was asymptomatic while the others had mild symptoms such as cough (n=19), fever (n=17), headache (n=13), gastrointestinal symptoms (n=4) and dyspnea (n=2). Patients were randomly treated with bamlanivimab/etesevimab (n=10), casirivimab/imdevimab (n=10), or sotrovimab (n=10), 3.5±1.7 days from diagnosis. None of the patients required hospitalization. All pre-infusion sera were negative for SARS-CoV-2 NtAb activity. In post-infusion sera, casirivimab/imdevimab, bamlanivimab/etesevimab and sotrovimab showed activity against the wild type variant (19,814 [17,459-23,471]; 6,792 [4,736-8328] and 456 [259-592]), the delta variant (58,858 [41,585-79,971]; 12,145 [10840-18667] and 1023 [798-1134]) and the delta AY.4.2 (58,602 [42,941-82960]; 11,067 [10757-12614] and 1,333 [708-1714]). Notably, sotrovimab was the only active treatment against the omicron variant (216 [118-233]) (Figure 1). Within each individual treatment group, the NtAb titers 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 titers to wild type, delta and delta AY.4.2 variants were higher than those to omicron within all the individual treatment groups (p=0.005 for all comparisons). Comparing treatments, casirivimab/imdevimab neutralizing titers were significantly higher than bamlanivimab/etesevimab and sotrovimab against the wild type, the delta and the delta AY.4.2 variants and bamlanivimab/etesevimab neutralizing titers were significantly higher than sotrovimab for the same variants (p<0.001 for all comparisons). When considering all the 30 post-infusion sera, a significant correlation was observed between NtAb titers to any pair of wild type, delta and delta AY.4.2 variants (p<0.001 for all comparisons), while NtAb titers to omicron correlated significantly only to NtAb titers to wild type virus (p=0.009) (Supplementary Figure 1).

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 the 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], while sotrovimab appears to retain activity against all the variants tested, including omicron, although reduced by 2.7-fold, similar to what reported in 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.

Author contributions

IV, MZ, DF and MRG conceived the idea for this work. FD, LF, VM, AL, 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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Transparency declaration

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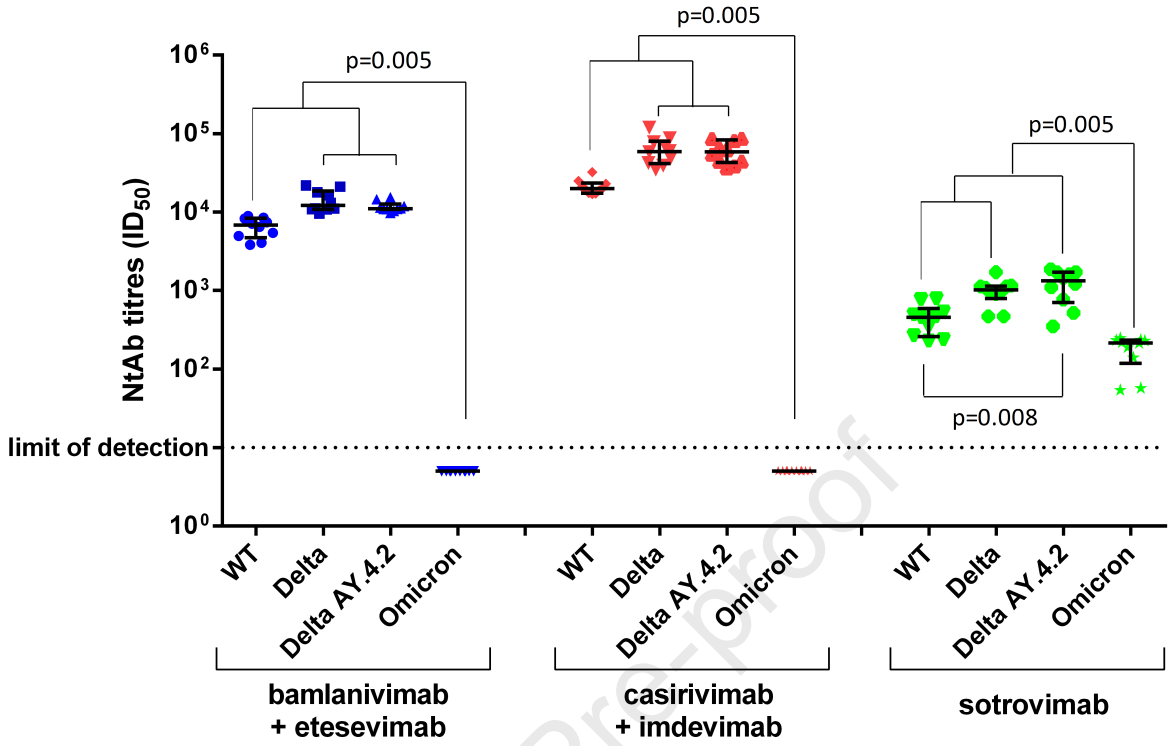

WT	6,792 [4,736-8328]	19,814 [17,459-23,471]	456 [259-592]
Delta	12,145 [10840-18667]	58,858 [41,585-79,971]	1023 [798-1134]
Delta AY.4.2	11,067 [10757-12614]	58,602 [42,941-82960]	1,333 [708-1714]
Omicron	<10	<10	216 [118-233]