Improved monoclonal antibody neutralization for Omicron sublineages BA.2.75, BF.7 and BQ.1

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Abstract

The mortality rate due to COVID-19 in immunocompromised cases is considerably high. Monoclonal antibody (mAb) therapy is essential in managing SARS-CoV-2 infection, especially in immunocompromised cases. The mutation in the spike protein RBD region of the SARS-CoV-2 leads to the substitution of amino acids resulting in an altered ACE2 binding affinity. The mAbs must be tested in-vitro using standard neutralisation assays designed against emerging SARS-CoV-2 variants to estimate the mAb therapy efficacy. Based on already available data on the mAb efficacy for known SARS-CoV-2 variants, it is plausible to draw inferences for other closely related SARS-CoV-2 variants in circulation owing to the similar spike protein RBD amino acid sequence. In this article, we have attempted to analyse the data of mAb efficacy tested against SARS-CoV-2 variants and extrapolate on other emerging omicron sublineages like BA.2.75, BF.7 and BQ.1.

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ABSTRACT: The mortality rate due to COVID-19 in immunocompromised cases is considerably high. Monoclonal antibody (mAb) therapy is essential in managing SARS-CoV-2 infection, especially in immunocompromised cases. The mutation in the spike protein RBD region of the SARS-CoV-2 leads to the substitution of amino acids resulting in an altered ACE2 binding affinity. The mAbs must be tested in-vitro using standard neutralisation assays designed against emerging SARS-CoV-2 variants to estimate the mAb therapy efficacy. Based on already available data on the mAb efficacy for known SARS-CoV-2 variants, it is plausible to draw inferences for other closely related SARS-CoV-2 variants in circulation owing to the similar spike protein RBD amino acid sequence. In this article, we have attempted to analyse the data of mAb efficacy tested against SARS-CoV-2 variants and extrapolate on other emerging omicron sublineages like BA.2.75, BF.7 and BQ.1.

INTRODUCTION: In December 2019, SARS-CoV-2 emerged as the etiological agent for the COVID-19 pandemic and continued to evolve. Various subvariant of SARS-CoV-2 B.1.1.529 (Omicron) emerged and dominated the pandemic since November 2021.[1] Some omicron subvariants have significantly dominated globally, like BA.1, BA.2, BA.2.75, BA.2.75.2, BA.4.6, BA.4/BA.5, BF.7, XBB, XBB.1, BQ.1, BQ.1.1, CH.1.1 and BJ.1. The international spread of SARS-CoV-2 lineages of concern can be tracked by accessing daily reports available at the website cov-lineage.[2] The report revealed that VOCs like BA.2.75, BQ.1 and BF.7 had spread significantly across the globe. BA.2.75 has been reported from India 70.0%, Australia

3.0%, United Kingdom (UK) 3.0%, Canada 3.0% and United States of America (USA) 6.0%; BQ.1 has been reported from USA 56.0%, Canada 7.0%, UK 6.0%, France 4.0% and Sweden 4.0%; BF.7 has been reported from USA 16.0%, Germany 17.0%, Denmark 10.0%, Belgium 6.0% and France 10.0%.

RESULTS & DISCUSSION: We observed that the spike protein RBD region's amino acid sequence for dominant omicron subvariants like BA.2.75, BQ.1 and BF.7 had significant similarities to the already studied BA.2.75.2, BQ.1.1 and BA.4 / BA.5, respectively (Figure A). Compared with subvariant BA.2.75, BA.2.75.2 contains three additional mutations, R346T, G482S and F486S, in the spike protein RBD region (Figure A). Compared with subvariant BQ.1, BQ.1.1 contains one additional mutation, R346T, in the spike protein RBD region (Figure A). Compared with subvariant BA.4/BA.5, BF.7 contains one additional mutation, R346T, in the spike protein RBD region (Figure A). The fact that the two dominating subvariant BA.2.75 and BQ.1 have no mutations at the R346 residue raises optimism that monoclonal antibodies may show improved efficacy. Earlier studies have shown that the efficacy of several therapeutic monoclonal antibodies (mAbs) was impaired because of mutation at the position R346K in an Omicron subvariant BA.1.1.[3,4]

Various reports are indicating higher COVID-19 mortality rates amongst immunocompromised patients. The morbidity and mortality weekly report (MMWR) published by CDC in July 2022 shows that the mortality rates of vaccinated and unvaccinated immunocompromised patients were reported to be 16.5% and 12.9%.[5] Another report from France that studied critically ill patients showed a mortality rate of 46.9% for Omicron infected immunocompromised patients compared to non-immunocompromised patients with a mortality rate of 26.2%.[6] A report from the UK by Turtle et al. revealed the mortality rate of immunocompromised hospitalised patients as 36% and 19% in the first COVID-19 wave and the fourth Omicron wave, respectively.[7] Belsky et al. analysed a mortality rate of 23.2% amongst COVID-19 patients who were immunocompromised and had undergone a solid organ transplant. Amongst immunocompromised cases in pediatric cancer patients and adult cancer patients, the mortality rate was observed to be 10.9% and 28.1%, respectively.[8]The rate of mortality is unusually high in the immunocompromised cases who have comorbidities; in such groups, the role of monoclonal antibody therapy is indispensable. The study conducted by Arora et al. emphasises the role of mAbs in managing SARS-CoV-2, especially in immunocompromised cases.[9]

As per the findings of the study conducted by Arora et al., it was revealed that all mAbs included in the study had shown efficient neutralisation against the B.1 pseudovirus particle (pp) possessing wild-type S protein RBD region.[9] The study establishes that the wild-type S protein RBD region is strongly correlated with the efficient neutralization of the virus by the mAbs. Considering this strong correlation, we propose extrapolating the findings of the mAb neutralisation assay for other SARS-CoV-2 omicron sublineages, which have a similar S protein RBD region amino acid sequence. In the study of Arora et al, bebtelovimab mAb efficiently neutralised the BA.2.75.2pp and Regdanvimab, and Sotrovimab mAbs poorly neutralised the BA.2.75.2pp. The S protein RBD region amino acid sequence for BA.2.75.2 is similar to BA.2.75, except at positions 346, 482 and 486 where BA.2.75 possesses wild-type amino acid (Figure A). This may imply that the wild-type at position 346 may impart efficient neutralisation against BA.2.75 when bebtelovimab is used. The wild-type at positions 486 and 346 may improve the neutralisation efficacy from poor to moderate against BA.2.75 when Regdanvimab and Sotrovimab are used, respectively. In the study of Arora et al, cilgavimab and bebtelovimab mAbs efficiently neutralised the BA.4/BA.5pp. Imdevimab mAb and Cilgavimab-Tixagevimab (cocktail mAbs) moderately neutralised BA.4/BA.5pp. The S protein RBD region amino acid sequence for BA.4/BA.5 is similar to BF.7, except at amino acid position 346, where BF.7 possesses a mutation R346T (Figure A). This may imply that the mutation at position R346T may reduce the neutralisation efficacy from efficient to moderate against BF.7 when bebtelomivab and cilgavimab are used. Similarly, the mutation at position R346T may also reduce the neutralisation efficacy from moderate to poor against BF.7 when imdevimab, and Cilgavimab-Tixagevimab (cocktail mAbs) are used. In the study of Arora et al, the BQ.1.1pp were not neutralised by any mAbs; all mAb neutralisation assays had EC50 values >50,000ng/ml. The S protein RBD region amino acid sequence for BQ.1.1 is similar to BQ.1, except at position 346, where BQ.1 possesses wild-type amino acid (Figure A). This may imply that no mutation at position 346 may improve the neutralisation efficacy for BQ.1.

A comparison of globally prevalent Omicron sublineages was performed for their respective RBD residues interacting with ACE2 against mAb EC50 values (Figure B). In total, 17 RBD residues that interact with ACE2 have been identified, out of which 8 positions had mutations, and 9 positions had no mutations across 14 Omicron sublineages. The analysis revealed that there are 8 positions of RBD residues with no mutations that interact with ACE2, which may continue to be efficiently targeted by mAbs. We further analysed the recent data reported by Arora et al which revealed that two mAbs, Sotrovimab and Romlusevimab, did not target any RBD residues interacting with ACE2 (Figure B). As per the supplementary table titled 'antibody information' in the article of Arora et al, it is declared under the mode of action that Sotrovimab- abrogates S protein driven entry at a post attachment step and Romlusevimab- abrogates S protein/ACE2 interaction. The information in the supplementary table and Figure S1 does not corroborate for Romlusevimab as no RBD residues interacting with ACE2 are represented in Figure S1. As per the report, even at the highest concentration Romlusevimab (IC50 >200 nM) did not compete with ACE2 for binding to RBD, implying that Romlusevimab does not block RBD residues interacting with ACE2.[10] This indicates that the information in the supplementary table of the article published by Arora et al, the proposed mode of action of Romlusevimab does not corroborate with the finding of our analysis.

The comparative analysis of mAb interacting at mutation positions in RBD revealed a strong correlation against neutralization assay for all mAbs except for Bamlanivimab, Etesevimab and Bebtelovimab which showed no correlation. The detailed correlation between the monoclonal antibody neutralisation assay and the mutation at the position in the spike protein RBD region is depicted in the Table.

METHOD: The neutralization efficacy of monoclonal antibodies against omicron subvariants was assessed by comparing the amino acid substitutions in the RBD region of SARS-CoV-2. The information on SARS-CoV-2 omicron subvariants that have significantly dominated globally was obtained from the emerging variants tool in Global Initiative on Sharing All Influenza Data (GISAID) (https://gisaid.org/). The data on the international spread of SARS-CoV-2 lineages were obtained from Cov-Lineages (https://cov-lineages.org). The information on the mutations leading to the amino acid substitution in the RBD region of the spike protein of SARS-CoV-2 lineages was obtained from outbreak.info SARS-CoV-2 data explorer (https://outbreak.info) and CoVariants (https://covariants.org). The information on the target and the mode of action for the SARS-CoV-2 monoclonal antibodies like Casirivimab[11-13], Imdevimab[11-13], Bamlanivimab[13-16], Etesevimab[13-16], Cilgavimab[13,17-19], Tixagevimab[13,17-19], Amubarvimab[13,20,21], Romlusevimab[13,20,21], Adintrevimab[22], Regdanvimab[13,23,24], Bebtelovimab[13,17,25-29] and Sotrovimab[13,27,28,30,31] was summarised in the Figure. The qualitative data analysis was performed using google spreadsheets.

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DECLARATION OF INTERESTS:

The authors declare no competing interests.

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TABLE:

Comparative analysis of mAb interacting at mutation positions in RBD to understand neutralization efficacy

mAb
Casirivimab (single mAb)
Imdevimab (single mAbs)
Cocktail mAbs
Bamlanivimab (single mAb)
Etesevimab (single mAb)

Cocktail mAbs
Cilgavimab (single mAb)

Tixagevimab (single mAb)

Cocktail mAbs
Amubarvimab (single mAb)

Romlusevimab (single mAb)

Cocktail mAbs
Regdanvimab (single mAb)

Bebtelovimab (single mAb)

Sotrovimab (single mAb)

Adintrevimab (single mAb)

indicates an increase in EC50 of cocktail mAbs as compared to single mAb. indicates a decrease in EC50 of

FIGURE LEGEND: Improved monoclonal antibody neutralization for Omicron sublineages BA.2.75, BF.7 and BQ.1

(A) A comparison of 14 globally most prevalent Omicron sublineages for their respective positions in the RBD region. The location of mutations in the RBD region of spike proteins of SARS-CoV-2 lineages is indicated in blue. RBD residues that interact with ACE2 are indicated in orange. Monoclonal antibodies (mAbs) targeting the epitope at RBD positions are indicated in red.

(B) A comparison of Omicron sublineages for only RBD residues interacting with ACE2 against mAbs. RBD residues that interact with ACE2 have been identified for 17 positions, out of which eight positions, as indicated in yellow, had mutations reported across Omicron sublineages, and nine positions, as indicated in green, had no mutations.