TITLE

Susceptibility of SARS-CoV-2 Omicron Variants to Therapeutic Monoclonal Antibodies: Systematic Review and Meta-analysis

SHORT TITLE: SARS-CoV-2 Omicron Variants and Monoclonal Antibodies

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ABSTRACT

SARS-CoV-2 Omicron variants contain many mutations in its spike receptor binding domain, the target of all authorized monoclonal antibodies (mAbs). Determining the extent to which Omicron variants reduced mAb susceptibility is critical to preventing and treating COVID-19. We systematically reviewed PubMed and three preprint servers, last updated February 22, 2022, of the *in vitro* activity of authorized mAbs against the Omicron variants. Thirty-three studies were eligible including 33 containing Omicron BA.1 susceptibility data and five that also contained Omicron BA.2 susceptibility data. The first two authorized mAb combinations, bamlanivimab/etesevimab and casirivimab/imdevimab, were inactive against the Omicron BA.1 and BA.2 variants. In 24 studies, sotrovimab (third authorized mAb) displayed a median 4.1-fold (IQR: 2.4-7.6) reduced activity against Omicron BA.1 and, in four studies, a median 26-fold (IQR:16-35) reduced activity against Omicron BA.2. In 18 studies, cilgavimab and tixagevimab independently displayed median reductions in activity of >300-fold against Omicron BA.1, while in ten studies, the cilgavimab/tixagevimab combination (fourth authorized mAb preparation) displayed a median 63-fold (IQR: 26-145) reduced activity against Omicron BA.1. In two studies, cilgavimab was approximately 100-fold more susceptible to BA.2 than to BA.1. In two studies, bebtelovimab, the most recently authorized mAb, was fully active against both the Omicron variants. Disparate results between assays were common as evidenced by a median 42-fold range (IQR: 25-625) in IC_{50} between assays for the eight authorized individual mAbs and three authorized mAb combinations. Highly disparate results between published assays indicates a need for improved mAb susceptibility test standardization or inter-assay calibration.

Key words: SARS-CoV-2, Omicron variant, Monoclonal antibody, Neutralization, Spike protein

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INTRODUCTION

Neutralizing antibodies (Abs) block the entry of virus into host cells and recruit host effector pathways to destroy virus-infected cells. Most SARS-CoV-2 neutralizing Abs identified in persons recovering from COVID-19 bind the surface exposed spike receptor binding domain (RBD) or N-terminal domain (NTD). The RBD is the main target of human neutralizing Abs and the sole target of those mAbs that have either received emergency use authorization by the U.S. Food and Drug Administration or are in advanced clinical development. The RBD, which encompasses residues 306–534, alternates between a closed/down position and an open/up position. When in the up position, it binds to the human ACE2 receptor. Approximately 20 RBD residues form contacts with the human ACE2 receptor [1]. The region of the RBD that contains these residues encompasses residues 438–506 and is called the receptor-binding motif, whereas the remainder of the RBD is called the RBD core.

Although no two SARS-CoV-2 neutralizing mAbs have identical epitopes, those binding the RBD have been grouped into several classes depending on the location of their binding residues and whether they can bind the RBD in its up and/or down position [2–4]. According to the most used classification, class I and II mAbs bind to amino acids contained within the receptor binding motif, while class III and IV mAbs bind solely or predominantly to the RBD core [3].

Five mAb preparations have been authorized by the U.S. FDA [5], two have been approved in other countries, and 13 others are in human clinical trials [6]. The combinations of bamlanivimab/etesevimab and casirivimab/imdevimab were approved for outpatient treatment and post-exposure prophylaxis in high-risk individuals. The combination of cilgavimab/tixagevimab was approved for pre-exposure prophylaxis in high-risk individuals. Sotrovimab and bebtelovimab were each approved for the outpatient treatment of high-risk individuals.

The Omicron BA.1 variant contains 15 RBD mutations including G339D, S371L, S373F, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, and Y505H. Mutations K417N, G446S, Q493R, G496S, Q498R, N501Y, and Y505H are located in the ACE2-binding site [1]. The Omicron BA.2 variant, which has been much less studied, contains three additional RBD mutations T376A, D405N, and R498S but does not contain G446S and G496S. Approximately 10% to 30% of Omicron BA.1 isolates also contain R346K. From previously published high-throughput studies in which all single RBD mutations were evaluated for their strength of binding to FDA-authorized mAbs, it was already known that that bamlanivimab/etesevimab (K417N, E484A, Q493R) and

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casirivimab/imdevimab (N440K, G446S, Q493R) would likely be inactive against the Omicron variant [7,8]. However, alone, none of the Omicron mutations were previously found to reduce susceptibility to cilgavimab, tixagevimab, sotrovimab, or bebtelovimab. Furthermore, because every combination of mutations cannot possibly be tested in advance, it was unclear what effect the mutations would have on these specific mAbs. We therefore systematically reviewed those studies that assessed the neutralizing activity of FDA-authorized mAbs against Omicron variants.

METHODS

We searched PubMed, BioRxiv, MedRxiv, and Research Square using the search terms "SARS-CoV-2 AND Omicron AND (Antibody OR Neutralization OR Therapy)" to identify studies in which SARS-CoV-2 Omicron variants were assessed for their neutralizing susceptibility to FDA authorized mAbs. We supplemented the data in these studies with data made available on an NIH website provided by two mAb manufacturers (https://opendata.ncats.nih.gov/covid19/). This is a living systematic review with the plan to update results, as more studies become available. For the analyses presented here, searches were last updated on February 22, 2022.

Each study was reviewed to determine the IC_{50} in ng/ml of mAbs against the Omicron variant and against wildtype SARS-CoV-2 variants defined as those lacking RBD mutations. In addition to susceptibility data for authorized mAbs, we also collected susceptibility data for mAbs that have been approved in another country or that were in a phase II or III clinical trial. For each study, the sequence of the wildtype variant and the RBD mutations in the Omicron variant were recorded. Mutations were defined as amino acid differences from the Wuhan-Hu-1 reference variant. Wildtype control variants were defined as including either the Wuhan-Hu-1 variant, an early clade A or B variant (including B.1 variants which contain the spike mutation D614G), or other variants lacking RBD mutations.

For each study, we recorded the following information about the assays employed to assess neutralizing activity: (i) whether the virus used to assess neutralization was an infectious virus isolate (also referred to as an "authentic virus") or a non-replication-competent pseudotyped virus; (ii) the cell line used to assess neutralization; (iii) the virus inoculum size; (iv) the duration of the assay; (v) the method used to assess either virus replication for authentic virus assays or cell entry for pseudotyped virus assays; and (vi) the highest mAb concentration employed and whether dose-response curves were included in the study's publication. Although some studies referred to the

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tested mAbs by their generic names and others by the name of their parent compounds, it was rarely known whether these mAbs differed from one another. Therefore, we referred to all such mAbs by their generic name.

All IC_{50}s were reported in ng/ml. For the purposes of analysis, IC_{50}s reported as being '>1,000 ng/ml' or as being above 10,000 ng/ml were both recorded as 10,000 ng/ml. IC_{50}s reported as being between 1,000 ng/ml and 10,000 ng/ml were recorded as the value provided by the study. Fold-reductions in susceptibility were not analyzed for two studies that used a Delta virus variant rather than a wildtype control virus variant. The degree of variation in the neutralizing activity of each mAb as measured in different studies was assessed using the median absolute deviation (MAD) from the median of the log_{10} transformed IC_{50}s. Outliers were defined as values that were more than 2 MADs from the median of the log_{10} transformed IC_{50}s. Outliers were included in calculating the median.

Screening for eligibility and data extraction was performed independently by two of the authors**.** Given the large between-study heterogeneity in several of the estimates, we focused on median and interquartile range, whenever appropriate rather than a formal quantitative synthesis with meta-analysis. However, as we were particularly interested in disparities between assays, we also reported the full range in susceptibility values between different assays for the same mAb. Each of the assay characteristics was perused as a source that might explain the heterogeneity between subgroups of studies, but no formal quantitative synthesis of subgroup data was performed because of the small number of studies sharing the same assay characteristics. The reporting of the overview follows the PRISMA guidelines [9]. The data for this project can be found on Github repository https://github.com/hivdb/covid-drdb-payload. The code for Figure 2 can be found at https://observablehq.com/@2a230210780ca54d/mab-neutralization-review.

RESULTS

Search results

As of February 22, 2022, 31 studies met the search criteria (Figure 1). Twelve of the studies were reported in a peer-reviewed publication [10–21]; 19 were published as preprints [22–40]. Two additional studies comprised data available on the NIH National Center for Advancing Translational Sciences (NCATS) SARS-CoV-2 Variants and Therapeutics open data portal [41,42]. Neutralizing data for the Omicron BA.1 variant alone was reported in 28

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studies while data for the Omicron BA.1 and BA.2 variants were reported in five studies [29,31,34,36,43]. Five studies also reported neutralizing susceptibility data for Omicron BA.1 with and without the RBD mutation R346K [10–12,26,29]. Four of the studies, used two different methods to determine neutralizing activity for one or more mAbs [13,26,29,44]. Therefore, results were available for one or more mAbs using 37 different neutralizing susceptibility assays. All but two studies used an early ancestral variant lacking any RBD mutation as a control. Most of these studies used an early variant containing D614G indicated as B.1 in Table 1. Two studies used a Delta virus variant as a control [14,21].

For the first two FDA authorized mAb preparations, data for bamlanivimab, etesevimab, or the combination bamlanivimab/etesevimab was reported in 22 studies while data for casirivimab, imdevimab, or the combination casirivimab/imdevimab were reported in 28 studies. For the third and fourth FDA authorized mAb preparations, data for sotrovimab were reported in 24 studies while data for cilgavimab, tixagevimab, or the combination of cilgavimab/tixagevimab were reported in 17 studies. Data for the most recently authorized mAb, bebtelovimab was reported in 3 studies.

Neutralizing susceptibility assays

Twelve of the neutralizing susceptibility assays used authentic virus isolates while 24 used pseudotyped viruses. One method used SARS-CoV-2 virus-like particles comprising the spike, nucleocapsid, matrix, and envelope structural proteins and a packaging signal-containing messenger RNA that together form RNA-loaded capsids capable of spike-dependent cell transduction [37]. Of the 24 assays using pseudotyped viruses, 13 employed an HIV-1 backbone, nine a VSV backbone, and two studies did not describe the pseudotyped virus (Table 1).

The spike mutations reported in each study were in nearly all cases identical to the prototype Omicron BA.1 sequence and contained the following mutations: NTD – A67V, del69-70, T95I, G142D, del143-145, del211, L212I, ins214EPE; RBD – G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H; CTD: T547K, D614G, H655Y, N679K, P681H; and S2: N746K, D796Y, N856K, Q954H, N969K, L981F. The few exceptions included one paper in which the Omicron sequence also contained A701V [18] and two publication in which the pseudotyped virus spike contained Q493K (rather than Q493R) [33]. At least two studies reported using pseudotyped viruses containing amino acid cytoplasmic tail truncations [33,34]. However, this is a

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common practice used to increase the expression of spike proteins [45] that may not have been consistently reported.

The most commonly used cell lines were Vero cells, Vero cells stably expressing TMPRSS2 or TMPRSS2 plus ACE2, and 293T cells stably expressing ACE2 or TMPRSS2 plus ACE2 (Table 1). Huh-7, HOS-ACE2-TMPRSS2, and U2OS-ACE2 cells were also used. Because Vero cells are intrinsically resistant to HIV-1 infection, they were not used in any of the assays using HIV-1 pseudotyped viruses. While most assays used ≥10,000 cells in 96 well plates, this information was not consistently reported. Similarly, the viral inoculum was also inconsistently reported (Table 1).

For infectious virus assays, virus replication was assessed based on microscopic cytopathological effects usually accentuated with SARS-CoV-2 immunostaining (e.g., focus-forming or plaque-reduction assays). For pseudotyped virus assays, entry into cells was measured as relative light units as each virus construct contained a luciferase reporter gene. For most assays, the highest mAb concentration was ≥ 10,000 ng/ml. However, in three assays the concentration was lower than 10,000 ng/ml, and the concentration used in three other assays was not reported (Table 1). Dose response curves were included for 19 of the 33 studies.

Omicron BA.1 variant neutralizing activity

Bamlanivimab/etesevimab and casirivimab/imdevimab: Figures 2A-F display the IC_{50}s against the Omicron BA.1 variant and a wildtype control for the mAbs in the first two FDA authorized mAb preparations: bamlanivimab, etesevimab, and the combination of bamlanivimab/etesevimab, and casirivimab, imdevimab, and the combination of casirivimab/imdevimab. In virtually all assays, the IC_{50} for each of these mAbs (alone and in combination) against Omicron was greater than 10,000 ng/ml and the reduction in their activity compared with control was approximately 1000-fold.

Sotrovimab: Figure 2G displays the IC_{50}s against the Omicron BA.1 variant and a wildtype control for sotrovimab (n=24 results from 24 studies), the third FDA EUA mAb preparation. For sotrovimab, the median wildtype IC_{50} was 78.2 ng/ml (range:8.4-1964; IQR: 33.5- 153.5) and the median Omicron BA.1 variant IC_{50} was 268 ng/ml (range: 57-7756; IQR: 174-383). There were two low (8.4 and 12 ng/ml) and two high (1168 and 1964 ng/ml) wildtype

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outlier IC_{50}s. There were three low (57 to 95 ng/ml) and five high (929 to 7756 ng/ml) outliers for Omicron BA.1. The median fold (Omicron BA.1 IC_{50} / wildtype IC_{50}) was 4.1 (range: 0.05-172; IQR: 2.5-7.4).

One study using an authentic virus assays reported highly disparate results depending on whether Vero-TMPRSS2 cells (wildtype IC_{50} = 202 ng/ml and Omicron BA.1 variant IC_{50} = 373 ng/ml) or Vero-TMPRSS2-ACE2 cells (wildtype IC_{50} = 1,168 ng/ml and Omicron BA.1 variant IC_{50} = 7,756 ng/ml) were used [13]. One outlier study reported that the Omicron BA.1 variant was more susceptible to sotrovimab than to the wildtype lineage B control (lacking the D614G mutation) [20]. Another outlier study reported a 172-fold reduction in susceptibility for the Omicron BA.1 variant compared with wildtype [33]. Except for these two outlier studies, there was a significant correlation between the wildtype and Omicron IC_{50}s for sotrovimab (r = 0.76; p = 0.00004).

Cilgavimab/tixagevimab: Figures 2H-J display the IC_{50}s against the Omicron BA.1 variant and a wildtype control for cilgavimab (n = 18 results), tixagevimab (n = 18 results), and the combination of cilgavimab/tixagevimab (n=10 results). For cilgavimab, the median wildtype IC_{50} was 5.8 ng/ml (IQR:3.7-35.3, range: 2-93 ng/ml) and the median Omicron BA.1 variant IC_{50} was 7,900 ng/ml (IQR:1,581-10,000; range: 382-10,000 ng/ml). The median cilgavimab fold was 362 (IQR:57.6-1,333, range:10.3-5,000). Among these 18 studies, there was no significant correlation between the IC_{50} for wildtype and the Omicron BA.1 variant.

For tixagevimab, the median wildtype IC_{50} was 2.0 ng/ml (IQR:1.6-8, range: 0.2-47 ng/ml) and the median Omicron BA.1 variant IC_{50} was 1,032 ng/ml (IQR:269-10,000, range: 88-10,000 ng/ml). There was one low (IC_{50} = 0.2 ng/ml) and two high (IC_{50} = 26 and 47 ng/ml) wildtype outliers. There were no Omicron BA.1 variant outliers. The median tixagevimab fold was 307 (IQR:95-2,325, range:16-10,000 ng/ml). There was no significant correlation between the IC_{50} for wildtype and the Omicron BA.1 variant.

For the combination of cilgavimab/tixagevimab, the median wildtype IC_{50} was 6.1 ng/ml (IQR:1.4-16.7 range:0.5-35 ng/ml) and the median Omicron BA.1 variant IC_{50} was 264.5 (range: 50.4-1,888 ng/ml). There were no wildtype outliers. For Omicron, there was one low (IC_{50}=50.4 ng/ml) and two high (IC_{50}=1,488 and 1,888 ng/ml) outliers. The median cilgavimab/tixagevimab fold was 62.6 (range:11.3-183). There was a suggestion for correlation between wildtype and the Omicron BA.1 variant IC_{50}s (r = 0.66; p = 0.04).

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Non-FDA authorized mAbs: Regdanvimab, C135, C144, and Brii-196 displayed little residual activity against the Omicron BA.1 variant (Figure 2K-N), Brii-198, and ADG20 retained partial activity (Figure 2O-Q), while bebtelovimab appeared fully active (Figure 2R).

Effects of Omicron BA.1 individual spike mutations on mAb susceptibility

Three studies evaluated the susceptibility of each of the individual Omicron BA.1 variant RBD mutations to between five and ten mAbs [11,33,38]. Six of the RBD mutations were found to reduce susceptibility to one or more mAbs ≥10-fold: (i) S371L reduced etesevimab susceptibility 3 to 31-fold, imdevimab susceptibility 4 to 25-fold [11,33,38], sotrovimab susceptibility 12 to 240-fold [11,33,38], Brii-196 susceptibility 18-fold [11], Brii-198 susceptibility 17-fold [11], and adintrevimab susceptibility 18-fold [11]; (ii) K417N reduced etesevimab susceptibility >100-fold [11,33,38] and casirivimab susceptibility 6 to 45-fold [11,33]; (iii) N440K reduced imdevimab susceptibility 22 to 246-fold [11,33]; (iv) G446S reduced imdevimab susceptibility >100-fold [11,33]; (v) E484A reduced bamlanivimab susceptibility >100-fold [11,33,38]; and (vi) Q493R reduced bamlanivimab susceptibility >100-fold [11,38], etesevimab susceptibility 16 to 46-fold [11,38], and casirivimab susceptibility 42-fold [11]. With the exception of the S371L, each of the above findings for the authorized mAbs are consistent with previously published binding [7,8,46] and neutralization (https://covdb.stanford.edu/page/susceptibility-data/) studies.

The susceptibility of pseudotyped viruses containing the prototypical Omicron BA.1 variant mutations plus R346K (also referred to as Omicron BA.1.1) was evaluated in six studies . In these studies, the addition of R346K was found to reduce cilgavimab [10,11] and Brii196 [11] susceptibility by more than 10-fold compared with Omicron BA.1 lacking R346K but to have no impact on sotrovimab susceptibility [11,12,29].

Effects of Omicron BA.2 on mAb susceptibility

Five studies evaluated the susceptibility of the Omicron BA.2 variant to one or more mAbs [29,31,34,36,43]. The BA.2 variant remained highly resistant to bamlanivimab, etesevimab, casirivimab, imdevimab, and tixagevimab. However, in the two studies of cilgavimab, this mAb was found to have just 1.7-fold [31] and 3.9-fold [29] reduced activity, in contrast to reductions of 382-fold [31] and 6944-fold [29] for the BA.1 variant. Sotrovimab was evaluated in four studies and was found to have between 12 and 35-fold reduced susceptibility (median of 21-fold)

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[29,31,36,43]. Adintrevimab and Brii-198 appeared to be approximately 10 and 20-fold less active against Omicron BA.2 [29,31] compared with Omicron BA.1 while bebtelovimab appeared to fully active against both Omicron variants [29,31].

Effect of method on neutralizing susceptibility

Disparities among assays for the Omicron BA.1 variant were wide as evidenced by a median 42-fold range (between lowest and highest IC_{50}) against wildtype variants for the seven individual authorized mAbs and the three authorized mAb combinations that were most commonly tested (i.e., excluding bebtelovimab which was tested in just 3 assays; Figure 1): bamlanivimab (32-fold), etesevimab (13-fold), bamlanivimab/etesevimab (25-fold), casirivimab (42-fold), imdevimab (42-fold), casirivimab/imdevimab (50-fold), sotrovimab (3583-fold), cilgavimab (694-fold), tixagevimab (625-fold), and cilgavimab/tixagevimab (33-fold). To determine whether the use of authentic viruses as opposed to pseudotyped viruses influenced susceptibility, we compared the median IC_{50} for these 10 individual and combination mAbs against wildtype virus for the 63 assays using authentic viruses (range of 4 to 8 assays per mAb) compared with the 114 assays using pseudotyped viruses (range of 5 to 17 assays per mAb). For 9 of the 10 mAb preparations, the median authentic virus IC_{50} was higher than the median pseudotyped virus IC_{50} ranging from 1.3 to 8.6-fold higher (median 2.8-fold). Although one study showed that the sotrovimab IC_{50} for both wildtype virus and omicron was higher when Vero-ACE2-TMPRSS2 cells were used than when Vero-TMPRSS2 cells were employed, we were unable to demonstrate whether cells that over-expressed ACE2 or TMPRSS2 consistently had different IC_{50}s than other cell lines.

DISCUSSION

There was a high degree of concordance among studies reporting the susceptibility of Omicron BA.1 to the mAbs bamlanivimab, etesevimab, bamlanivimab/etesevimab, casirivimab, imdevimab, casirivimab/imdevimab, regdanvimab, C135, and C144 because, in virtually all cases, the IC_{50}s for these mAbs were above the upper limits of quantification. However, there was a high degree of disparity among studies reporting the susceptibility of Omicron BA.1 to the mAbs cilgavimab, tixagevimab, cilgavimab/tixagevimab, and sotrovimab. For these mAbs, studies reported IC_{50}s and fold reductions in susceptibility that often differed by as much as 100-fold.

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Although far fewer data were available for the Omicron BA.2 variant, two main differences from the BA.1 variant were observed. The median fold reduced susceptibility to sotrovimab which was 4.1-fold for BA.1 in 24 studies, was 21-fold for BA.2 in four studies. In contrast, the median fold reduced susceptibility to cilgavimab which was 382-fold for BA.1 in 19 studies, was 2.8-fold for BA.2 in two studies [29,31]. Only one clinical stage mAb, bebtelovimab, was active against both Omicron variants. Despite limited clinical efficacy data, bebtelovimab was authorized for the outpatient treatment of high-risk patients with COVID-19 primarily based on its *in vitro* activity [47]. As of this writing, there have been no structural studies that explain precisely how the binding mode of bebtelovimab avoids Omicron BA.1 and BA.2 mutations or how the reintroduction of glycines at positions 446 and 496 in Omicron BA.2 restores cilgavimab neutralizing activity.

Neutralization assays can be characterized by several variables including the nature of the virus preparation, the cell line used, the size of the virus inoculum, and the duration and means of quantifying virus entry into cells [48,49]. The two main types of virus preparation employed in the studies reviewed here were pseudotyped and authentic virus assays. A previous meta-analysis of the neutralizing susceptibility of Omicron to the polyclonal Abs in the plasma from convalescent and/or vaccinated individuals reported that pseudotyped virus assays yielded two-to-three times higher geometric mean titers compared with authentic virus assays for certain subpopulations [50]. Our comparison of the IC_{50}s of the most common mAb preparations against wildtype variants supported this observation showing a median 2.8-fold increased IC_{50} for assays performed using authentic viruses.

The nature of the virus preparation influences several additional aspects of neutralization assays. Authentic virus assays are influenced by differences in virus mutations outside of the spike gene and potentially by mutations that arise during the process of virus isolation. Although complete genomic sequence data were not available for all of the virus isolates studied, the reported spike sequences were nearly identical in all assays with minor differences reported in just two studies [18,33]. Authentic virus assays may also be more likely to be affected by the duration of virus culture if cell-to-cell spread is not restricted whereas pseudotyped viruses replicate only in the first cell they enter. Finally, authentic virus assays measure cytopathic effect usually augmented by immunostaining of virally infected cells while pseudotyped virus assays measure relative light units produced by luciferase-encoding reporter genes

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The most commonly used cell lines were African green monkey kidney epithelial Vero cells and human embryonic kidney (HEK) 293T cells. As Vero cells are resistant to HIV-1 infection, 293T cells were used for all pseudotyped HIV-1 assays. Depending on the study, both types of cells were modified to over-express ACE2, TMPRSS2, or both receptors (Table 1). Although it was not possible to discern an overall effect of cell line on IC_{50} values, one study showed that the sotrovimab IC_{50} against both wildtype and Omicron viruses was higher for Vero-ACE2-TMPRSS2 cells than for Vero-TMPRSS2 cells [13], which is consistent with an observation from another study which reported that the IC_{50} of sotrovimab against wildtype isolates was lowest for Vero and Huh7 cells and highest for cells over-expressing ACE2 [51]. That study also proposed that part of the activity of sotrovimab may be related to its inhibition of the interaction of spike and transmembrane lectins, which function as attachment inhibitors [51].

With the exception of one study, the choice of the wildtype control variant did not appear to impact mAb susceptibilities [20]. In this study, the susceptibility of a wildtype lineage B virus lacking D614G was less susceptible to sotrovimab than the Omicron BA.1 variant (which does contain D614G). One previous study has reported that sotrovimab was 162 times more active against pseudotyped viruses containing D614G compared to those lacking this mutation [52]. However, in our systematic review, sotrovimab was not found to consistently have reduced activity against control viruses lacking D614G (Table 1).

The size of the virus inoculum influences the IC_{50} for an antiviral agent by shifting the dose response curve. However, the virus inoculum size was not consistently reported either for the authentic or pseudotyped virus assays. Moreover, when it was reported, different measurements were employed. Authentic virus assays reported the virus inoculum size as either a 50% tissue culture infectious dose ($TCID_{50}$), the number of focus-forming units, or a multiplicity of infection. Pseudotyped virus assays reported the inoculum size as a $TCID_{50}$ or as the number of relative light units. Establishing a relationship between virus inoculum and IC_{50} was further complicated because the use of a highly permissive cell line may have the same effect as using a larger virus inoculum.

One might expect that the fold difference between Omicron and wildtype would be more consistent between studies than IC_{50} values because the distinct characteristics of an assay would be expected to influence the IC_{50} values of both the Omicron and wildtype control variant. To some extent, this was true. For sotrovimab, the fold difference between the Omicron BA.1 variant and wildtype ranged between 1.8 and 11-fold with the exception of two assays for which the fold differences were 0.05 [20] and 170 [33]. For the combination of

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cilgavimab/tixagevimab, the fold difference between Omicron BA.1 and wildtype ranged between 11 and 180-fold, without any results meeting our methodological criteria for being an outlier.

There is a long tradition of considering findings about the level of *in vitro* antiviral resistance to be clinically significant and informative. However, demonstrating this in SARS-CoV-2 clinical trials will be difficult because of the hesitancy to use drugs with reduced *in vitro* activity in a clinical trial and because of the rapidly changing spectrum of circulating SARS-CoV-2 variants. Considering the reduced activity of both sotrovimab and cilgavimab/tixagevimab against Omicron *in vitro* and the difficulty in performing variant-specific clinical trials, the efficacy of these mAbs against Omicron should be assessed in animal models as has been done for casirivimab/imdevimab [53].

In the treatment of viruses with reduced susceptibility, pharmacokinetics attain greater clinical significance because if the obtainable antiviral levels in patients are insufficient, viral suppression may not be possible. For sotrovimab, the geometric mean C_{max} in approximately 300 patients following a one-hour 500 mg intravenous infusion was 117.6 ug/ml with concentrations decreasing to 24.5 ug/ml after one month [54]. For cilgavimab/tixagevimab, the C_{max} following an intramuscular injection of 150 mg of each mAb was 16.5 and 15.3 ug/ml, respectively, with levels between 4 and 6 ug/ml being present for as long as six months. Thus, the very high concentrations achievable with these SARS-CoV-2 mAbs, well above the median Omicron IC_{50}s, may mitigate their reduced activity. Although the FDA emergency use authorization process does not allow flexibility in dosing, it is possible that better outcomes against Omicron variants could be obtained with higher dosages of sotrovimab and of cilgavimab/tixagevimab. Indeed, SARS-CoV-2 mAb dosages considerably higher than those approved for sotrovimab and cilgavimab/tixagevimab were used in phase III clinical trials for bamlanivimab/etesevimab (2800 mg for each mAb) [55] and casirivimab/imdevimab (2400 mg for each mAb) [56].

For most antiviral agents, combination therapy has been beneficial because each agent prevents the emergence of resistance to the other agent. However, the *in vitro* synergy between cilgavimab and tixagevimab may reflect the fact that both mAbs can simultaneous bind to the spike RBD at non-overlapping epitopes [57]. How often both mAbs bind simultaneously to the trimeric spike *in vivo*, however, is likely to be difficult to determine.

Some limitations of our review should be discussed. We included data from peer-reviewed papers, preprints, and one database and thus some included information is not fully peer-reviewed. Moreover, it is possible that additional studies with relevant results have remained unavailable to-date, but there is no strong reason to

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suspect that their findings would be systematically different from those that were available for this review. Moreover, in a rapidly emerging field, early results may have more heterogeneity than when the full picture emerges (consistent with the Proteus phenomenon) [58]. Finally, some study characteristics were not sufficient in full detail.

In conclusion, the marked variability in results reported in different studies is concerning and complicates the interpretation of published findings. Because many methodological aspects can influence neutralizing susceptibility, we were unable to determine the reason for the disparities between assays for the activity of the same mAb or mAb combination against wildtype viruses and the Omicron variant. One approach would be to standardize the method for assessing neutralizing activity [49]. Another approach is to use an external standard, such as that provided by the World Health Organization (WHO) to calibrate the results of assays performed under different conditions [49,59]. However, this reagent's limited and non-renewable nature currently limits its widescale utilization [60]. The marked loss of activity of many mAbs against the Omicron variant also underscores the importance of developing mAbs that target conserved regions of spike that are not targeted by the Abs produced in infected persons.

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FIGURE LEGENDS

Figure 1

Flow chart of study selection process. Of 439 de-duplicated studies identified through a search of PubMed and three preprint servers using the search string "SARS-CoV-2 AND Omicron AND (Neutralization OR Antibody OR Treatment)" 64 were read in their entirety following an initial review of titles and abstracts. 31 studies met our inclusion criteria in that they contained neutralizing susceptibility data for one or more FDA authorized monoclonal antibodies (mAbs). Two additional datasets, available on the NIH NCATs website were identified via press releases. The number of studies containing susceptibility data for the Omicron BA.1 and BA.2 variants and the number of results for each of the clinical stage mAbs is shown. Abbreviations: BAM (bamlanivimab), ETE (etesevimab), CAS (casirivimab), IMD (imdevimab), SOT (sotrovimab), CIL (cilgavimab), TIX (tixagevimab), REG (regdanvimab), ADI: (adintrevimab), BEB (bebtelovimab). The presence of two mAbs separated by "/" indicates the combination was tested or that each individual mAb in the combination was also tested.

Figure 2

Neutralizing susceptibility to the Omicron BA.1 variant for 18 individual mAbs or mAb combinations. Each plot shows the IC_{50}s of the wildtype control variant (on the left) connected by a line to the IC_{50}s of the Omicron BA.1 variant (on the right) performed in the same study. IC_{50}s at or above 10,000 ng/ml or recorded as being above ">1,000 ng/ml" are plotted as 10,000 ng/ml. Three values below 1 ng/ml for tixagevimab are plotted at 1 ng/ml. The distribution of fold-reductions in susceptibility is shown beneath each plot. Two studies that used a delta variant control are not included in the plots [14,21].

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Table 1. Descriptive Overview of the Neutralizing Susceptibility Assays and the Monoclonal Antibodies (mAbs) Undergoing Testing

Author	Control	Virus Type[1]	Cells[2]	Inoculum[3]	Hours	[Highest] (ug/ml)	Variants	mAbs[4]
Aggarwal21 [22]	A.2.2	Infectious	Vero	10^4 $TCID_{50}$	24	-	BA.1	BAM, CAS, IMD, SOT, CIL, TIX
Boschi22 [23]	B.1	Infectious	Vero	-	48	3.5	BA.1	BAM/ETE, CAS/IMD
Cao22 [29]	B	Infectious	Vero	10^2 $TCID_{50}$	120	10	BA.1	SOT, ADG20
Dejnirattisai22 [18]	B	Infectious	Vero	10^2 FFU	-	10	BA.1	BAM, ETE, CAS, IMD, SOT, CIL/TIX, ADI
Duty22 [26]	B.1	Infectious	Vero	10^2 FFU	-	-	BA.1, BA.1.1	CIL/TIX, SOT
Meng22 [21]	Delta	Infectious	HOS-ACE2-TMPRSS2	10^2 FFU	24	10	BA.1	CAS/IMD
Planas21c [14]	Delta	Infectious	U2OS-ACE2	0.001 MOI	20	10	BA.1	BAM/ETE, CAS/IMD, SOT, CIL/TIX
Takashita22 [19]	A	Infectious	Vero-TMPRSS2	10^3 FFU	24	50	BA.1	BAM, ETE, CAS, IMD, SOT, CIL/TIX
Touret22 [24]	B.1	Infectious	Vero-TMPRSS2	-	48	10	BA.1	BAM, ETE, CAS, IMD, SOT, CIL/TIX, REG
VanBlargan22-1 [13]	B.1	Infectious	Vero-TMPRSS2	10^2 FFU	70	10	BA.1	BAM/ETE, CAS/IMD, SOT, CIL/TIX, REG
VanBlargan22-2 [13]	B.1	Infectious	Vero-ACE2-TMPRSS2	10^2 FFU	24	10	BA.1	BAM/ETE, CAS/IMD, SOT, CIL/TIX, REG
Wilhelm21b [25]	-	Infectious	-	4 x 10^3 $TCID_{50}$	48	2	BA.1	CAS/IMD
Cameroni21 [12]	B.1	PV (VSV)	Vero	-	20	10	BA.1, BA.1.1	BAM/ETE, CAS/IMD, SOT, CIL/TIX, REG
Cao21 & Cao22 & Cui22 [10,17,29]	B.1	PV (VSV)	Huh-7	10^3 $TCID_{50}$	24	10	BA.1, BA.1.1, BA.2	BAM, ETE, CAS, IMD, SOT, CIL, TIX, Brii-196
Cathcart22 [40]	-	PV (VSV)	Vero	2 x 10^3 FFU	6	20	BA.1, BA.1.1, BA.2	SOT
NIH-NCATS21-1 (AstraZeneca) (FDA) [41]	B	PV (HIV)	293T-ACE2-TMPRSS2	10^6 RLU	48	10	BA.1	CIL/TIX
NIH-NCATS21-2 (AstraZeneca) (Monogram) [41]	B	PV (HIV)	293T-ACE2-TMPRSS2	10^4 – 5 x 10^5 RLU	72	-	BA.1	CIL/TIX
NIH-NCATS21 (Brii Biosciences) [42]	B	PV (HIV)	-	-	-	-	BA.1	Brii-196, Brii-198, Brii-196/Brii-198

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Chen22 [30]	A	PV (HIV)	293T-ACE2-TMPRSS2	-	72	1	BA.1	BAM/ETE, CAS/IMD
Duty22 [26]	B.1	PV (VSV)	293T-ACE2-TMPRSS2	-	-	-	BA.1, BA.1.1	CIL/TIX, SOT
Gruell22 [20]	B	PV (HIV)	293T-ACE2	-	48	10	BA.1	BAM/ETE, CAS/IMD, SOT
Hoffmann22 [15]	B.1	PV (VSV)	Vero	-	16	10	BA.1	BAM/ETE, CAS/IMD, SOT
Ikemura21 [27]	B.1	PV	293T-ACE2	-	48	10	BA.1	CAS/IMD, SOT
Ju22 [28]	B	PV (HIV)	293T-ACE2	-	48	50	BA.1	ETE, CAS/IMD, SOT, C144
Liu21l & Iketani22 [11,31]	B.1	PV (VSV)	Vero	-	10	-	BA.1, BA.1.1, BA.2	BAM/ETE, CAS/IMD, SOT, CIL/TIX, Brii-196/Brii-198, ADI
Sheward21 [32]	B.1	PV (HIV)	293T-ACE2	5 x 10^4 RLU	48	1	BA.1	BAM, ETE, CAS, IMD, SOT
Tada21f & Zhou22 [33,34]	B.1	PV (HIV)	293T-ACE2	2 x 10^3 $TCID_{50}$	48	1	BA.1, BA.2	BAM/ETE, CAS/IMD, SOT
Wang22 [16]	B.1	PV (VSV)	Vero	-	24	10	BA.1	BAM, ETE, CAS, IMD, SOT, CIL, TIX, REG, ADI
Wang22b [39]	B	PV (HIV)	293T-ACE2	-	48	50	BA.1	IMD, SOT
Zhou21e [38]	B.1	PV (HIV)	293T-ACE2-TMPRSS2	-	72	10	BA.1	BAM, ETE, CAS, IMD, SOT, CIL, TIX, BEB, REG, ADI, C135, C144
Westendorf21 [35]	B.1	PV (HIV)	293T-ACE2 or ACE2-TMPRSS2	-	72	-	BA.1	BAM, ETE, CAS, IMD, SOT, CIL, TIX, BEB, REG, ADI, C135, C144
Yamasoba22 [36]	B.1	PV (HIV)	HOS-ACE2-TMPRSS2	2 x 10^4 RLU	48	10	BA.1, BA.2	CAS/IMD, SOT
Syed21 [37]	B.1	VLP	293T-ACE2-TMPRSS2	-	24	20	BA.1	CAS, IMD

Footnote: [1]PV: pseudotyped virus using either HIV or vesicular stomatitis virus (VS); VLP: virus-like particle. [2]Cell line followed by ACE2 and/or TMPRSS2 indicates that the cells were modified to stably express these surface proteins. [3]$TCID_{50}$: 50% tissue-culture infectious dose; MOI: Multiplicity of infection; FFU: focus-forming units; RLU: relative light units. [4]BAM: bamlanivimab, ETE: etesevimab, CAS: casirivimab, IMD: imdevimab, SOT: sotrovimab, CIL: cilgavimab, TIX: tixagevimab, BEB: bebtelovimab, REG: regdanvimab, ADI: adintrevimab. The presence of two mAbs separated by "/" indicates the combination was tested and each individual mAb in the combination was also tested. "-": indicates the relevant data could not be identified. Cameroni21 also used an infectious virus for SOT and reported IC_{50}s that were nearly the same as wildtype in three assays. In Zhou21e, 293T-ACE2 cells were used for TIX and 293T-ACE2-TMPRSS2 used for CIL. Westendorf21 used infectious viruses as well as pseudotyped viruses for BEB.

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Figure 1

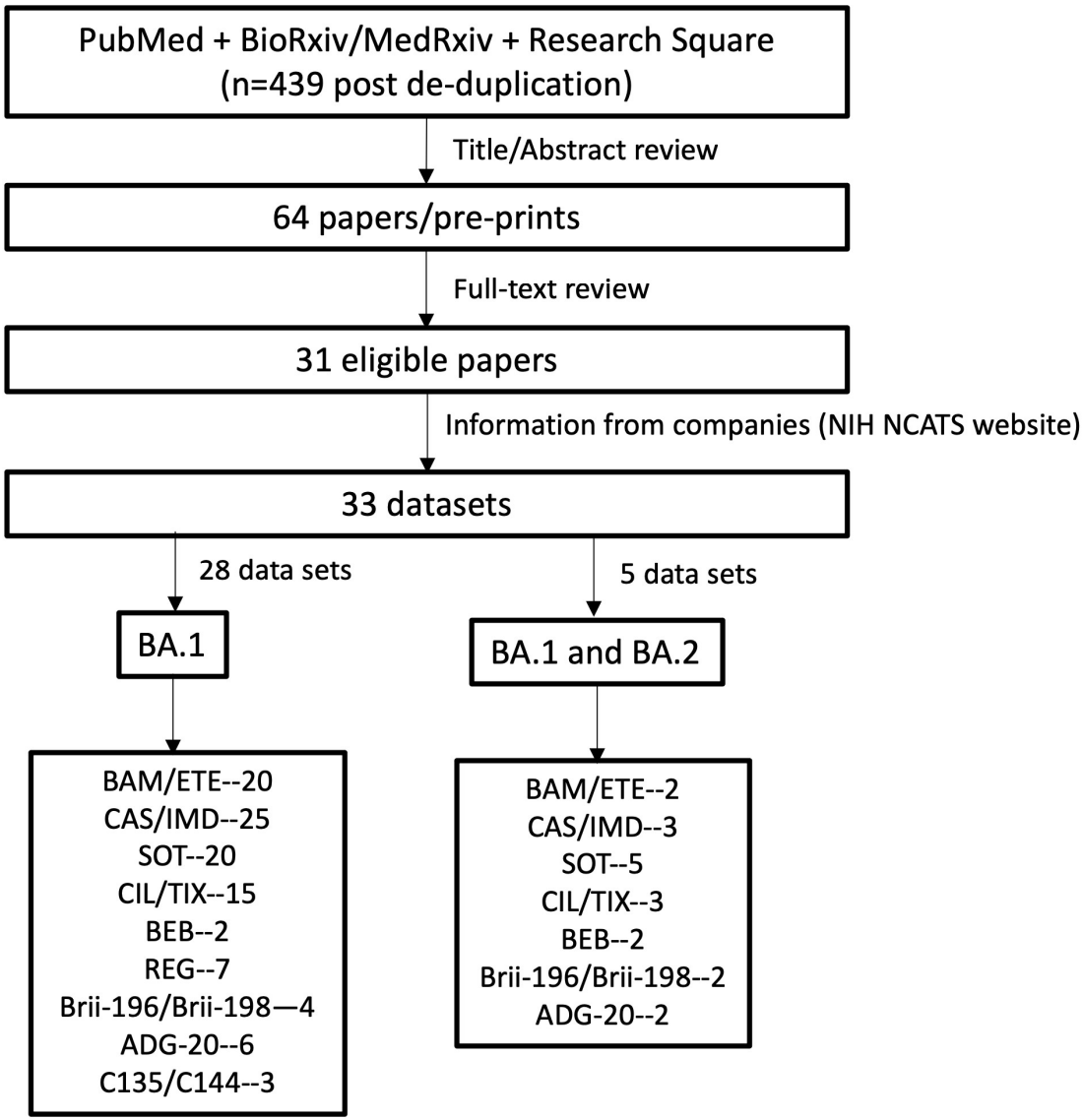

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Figure 2