

Monoclonal Antibodies for Early Treatment of COVID-19 in a World of Evolving SARS-CoV-2 Mutations and Variants

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Monoclonal antibodies targeting the receptor binding domain (RBD) of severe acute respiratory syndrome coronavirus 2 spike protein are important outpatient treatment options in coronavirus disease 2019 to mitigate progression of disease and prevent hospitalization. The impact of different RBD mutations on the efficacy of the available monoclonal antibodies and processes for incorporating this impact into treatment algorithms are ill defined. Herein, we synthesize the data surrounding the impact of key RBD mutations on the efficacy of US Food and Drug Administration Emergency Use Authorized monoclonal antibodies and describe our approach at Michigan Medicine at monitoring mutation frequency in circulating virus and developing an algorithm that incorporates these data into outpatient treatment pathways.

Keywords. bamlanivimab; bamlanivimab and etesevimab; casirivimab and imdevimab; COVID-19; SARS-CoV-2; variants.

Monoclonal antibodies (bamlanivimab [BAM], bamlanivimab + etesevimab [BAM-ETE], and casirivimab + imdevimab [CAS-IMD]) are available under Emergency Use Authorization (EUA) for early outpatient treatment of mild–moderate coronavirus disease 2019 (COVID-19) [1–3]. They have been shown to reduce the incidence of hospitalization and death in individuals at high risk for progression to severe disease, with a number

needed to treat (NNT) of roughly 20 patients to prevent 1 hospitalization [2].

These agents were selected for development based on neutralizing activity against viruses bearing “Wuhan-1-like” or D614G severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike proteins, and their efficacy to date has been assessed in settings where D614G predominated. Numerous variants of concern (VOC) or interest (VOI) with key mutations to the receptor binding domain (RBD) of the Spike protein have since emerged. These mutations may impact the efficacy of these agents, as the RBD is the target site for all currently authorized monoclonal antibodies [1–3]. Furthermore, these same RBD mutations have also been identified, and may be present, in viruses from lineages distinct from the main VOC/VOI.

It is important that monoclonal antibody programs consider the impact of mutations and local epidemiology of circulating virus when choosing monoclonal antibody products for use in their treatment algorithms. However, this is challenging for many reasons. First, SARS-CoV-2 genomic surveillance is incomplete and varies from state to state, and many data sources are not readily available or easy to understand. Second, while the information provided in the updated Food and Drug Administration (FDA) EUA fact sheets includes information on the impact of mutations on the neutralizing activity of monoclonal antibodies [1–3], the fact sheets do not offer usable guidance that can be applied to treatment decisions. Furthermore, it is unclear what considerations (ie, incidence of mutations locally, level of comparative “resistance” across available monoclonal antibodies, and available supply of monoclonal antibodies) should lead to preferential use of 1 agent over another. Herein, we describe the approach of the monoclonal antibody program at Michigan Medicine (Figure 1).

In order to develop a rational treatment strategy, the first step is to understand the impact that different variants and individual mutations have on the treatment options. This can be accomplished by assessing the impact of key RBD mutations on the the half maximal inhibitory concentration (IC_{50}) (concentration necessary to neutralize 50% of the virus) and IC_{80} values for each monoclonal antibody (Table 1) [4–7]. For some of the variants, the impact on the EUA monoclonals is straightforward. The N501Y mutation, which is the RBD mutation present in the B.1.1.7 strain, does not significantly impact any of the 4 approved monoclonal antibodies; thus, all products are appropriate treatment options [4, 5]. For both the B.1.351 and P.1 strains, BAM, ETE, and CAS all lose inhibitory activity against the combination of RBD mutations present (N501Y, E484K, and K417N(T)), and only CAS-IMD would be expected to be effective due to the retained activity of imdevimab in the setting of these mutations [4–6].

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Michigan Medicine Approach:

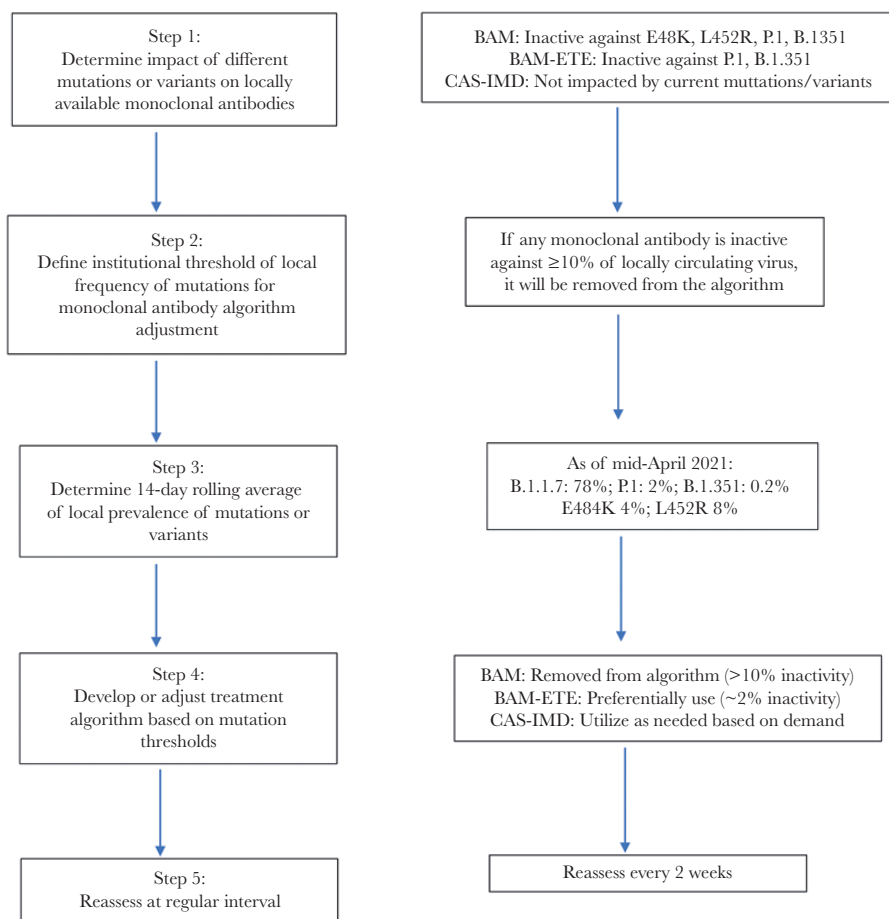


Figure 1. Approach for determining treatment algorithm for monoclonal antibodies based on locally circulating virus. Abbreviations: BAM, bamlanivimab; CAS, casirivimab; ETE, etesevimab; IMD, imdevimab.

The data are less clear for other variants or viruses bearing individual mutations. When E484K is the only RBD mutation present, as in P.2 and B.1.526, BAM loses activity, while CAS-IMD retains activity. ETE, and thus the BAM-ETE combination, is more complicated. The ETE IC_{50} is 2–3-fold higher against viruses with E484K when compared with wild-type

[4, 5]. While the IC_{50} is higher than that of IMD, it still remains relatively low at $<0.1 \mu\text{g/mL}$ [4], given that the mean peak concentration after a 1400-mg dose of ETE is $504 \mu\text{g/mL}$ [2]. Additionally, the ETE IC_{80} against E484K mutants is 1.3- and 3.4-fold lower than that of CAS and IMD, respectively [4]. Therefore, it is expected that BAM-ETE would remain a

Table 1. Impact of RBD Mutations on the Activity of EUA Monoclonal Antibodies

RBD Mutation ^a									Anticipated Activity		
	Bamlanivimab		Etesevimab		Casirivimab		Imdevimab		BAM	BAM—ETE	CAS—IMD
	IC_{50}	IC_{80}	IC_{50}	IC_{80}	IC_{50}	IC_{80}	IC_{50}	IC_{80}			
D614G	0.003	0.011	0.031	0.083	0.005	0.016	0.020	0.412	+	+	+
N501Y	0.008	0.022	0.043	0.372	0.007	0.020	0.044	0.340	+	+	+
E484K	>10	>10	0.062	0.234	0.202	0.786	0.018	0.304	-	+	+
K417N E484K N501Y	>10	>10	>10	>10	>10	>10	0.025	0.370	-	-	+
L452R	>10	>10	0.018	0.107	0.006	0.022	0.215	1.172	-	+	+

Abbreviations: BAM, bamlanivimab; CAS, casirivimab; ETE, etesevimab; EUA, Emergency Use Authorization; IC, the half maximal inhibitory concentration; IMD, imdevimab; RBD, receptor binding domain.

^aAll mutations are in addition to D614G; IC_{50} and IC_{80} values adapted from Wang et al. [4].

similarly effective option compared with CAS-IMD in the setting of E484K. It is important to note, when assessing BAM-ETE activity against E484K, that N501Y also slightly impacts the activity of ETE, causing a 1–3-fold increase in IC₅₀ values [4, 5]. B.1.1.7 strains have been reported to occasionally acquire the E484K mutation, and the impact of this combination of mutations on ETE activity has not been assessed. Given BAM's inactivity in the setting of E484K and the potential aggregate effect of N501Y and E484K to decrease the potency of ETE, the activity of BAM-ETE for the E484K and N501Y combination is unknown, and caution is warranted.

The L452R mutation, which is present in B.1.427/B.1.429 and B.1.526.1, leads to inactivity of BAM. Wang and colleagues demonstrated that L452R had no impact on ETE or CAS IC₅₀/IC₈₀ values, but increased IMD values ~5–7-fold [4]. While a separate publication recently suggested a ~7-fold increase in ETE IC₅₀ with B.1.427, the IC₅₀ remained <0.1 µg/mL, which was similar to that of CAS and lower than that of IMD [7]. Taken together, these studies suggest that both combination products (BAM-ETE and CAS-IMD) will be equally effective against the L452R mutation.

Given the impact that various mutations and variants have on monoclonal antibody activity, the next step is to understand circulating virus locally. Given the time-sensitive nature of treatment with monoclonal antibodies, it is not possible to perform real-time sequencing of infecting virus to inform patient-level monoclonal antibody decisions, and therefore focus needs to be shifted to local genomic surveillance. At the University of Michigan, our research laboratory receives an aliquot of all positive patient samples from the health system's clinical microbiology laboratory. All isolates with RT-qPCR cycle threshold values <30 are then sequenced. These data are then used to create rolling 14-day averages of key RBD mutations, both individually and in combination. Both are important, as these mutations will impact the efficacy of monoclonal antibody treatments regardless of whether they are present on a specific VOC.

Next, the monoclonal antibody team must utilize these data, in combination with current supply of BAM, BAM-ETE, and CAS-IMD to determine appropriate monoclonal antibody allocation and usage. While it may seem attractive to simply use CAS-IMD due to activity against all major globally circulating variants, we do not favor this strategy for 2 main reasons. First, supplies of CAS-IMD are limited, and it is not be feasible to administer that combination to everyone. Second, should B.1.351 or P.1 become prominent, CAS-IMD is the only currently available option for treatment, and it is important to be cognizant of that potential future reality.

At the University of Michigan, the assessment consists of continual analyses of the mutation and variant data locally. As of mid-April 2021, B.1.1.7 is common, rising, and representative of roughly 80% of the viruses locally. Fortunately, N501Y

does not impact the activity of any EUA monoclonal antibodies. The other 2 significant mutations currently present in the local strains are E484K (4% of strains) and L452R (8% of strains). To date, B.1.351, P.1, and B.1.1.7 with the E484K mutation remain rare and collectively represent <3% of circulating virus locally. No other combinations of the key mutations to the RBD have been identified.

As both E484K and L452R will render BAM ineffective and there is adequate supply of both BAM-ETE and CAS-IMD, we have discontinued BAM monotherapy. As for combination therapy, the in vitro evidence supports both BAM-ETE and CAS-IMD as appropriate treatment options based on the aforementioned activity of ETE against both E484K and L452R. Therefore, our current process is to preferentially utilize BAM-ETE as supplies are available to “reserve” CAS-IMD should the situation change. However, we also utilize CAS-IMD as needed based on the number of patients requiring treatment.

An important consideration for monoclonal antibody programs is to determine at what threshold percentage of circulating “resistance” to BAM-ETE there would be a need to switch to preferential use of CAS-IMD. As supply issues make it impossible for an early switch to CAS-IMD for all patients (eg, at the first signs of local B.1.351/P.1 circulation), it is informative to consider the impact that resistance would have on the NNT. The phase III trials report a decrease in the need for hospitalization in the high-risk population for which the EUAs were granted, from roughly 7% to 2% (NNT, 20) [2].

Table 2 displays the impact that the frequency of mutations circulating locally and the impact of said mutations on the efficacy of a monoclonal antibody product would have on the NNT to prevent a hospitalization. Performing such an analysis further supports not overreacting to the modest IC₅₀ increases to ETE with E484K or L452R. Even in a hypothetical scenario, where the slightly higher IC₅₀ values demonstrated with ETE with E484K and possibly with L452 render BAM-ETE 25% less effective against strains with these mutations, at a local rate of 10%–15% of circulating viruses, this would only increase the NNT to prevent a hospitalization from 20 to 21.

At Michigan Medicine, the cutoff for discontinuation of BAM-ETE has arbitrarily been set at a 10% increase in the NNT (or to an NNT of 22 or higher) for 2 main reasons. First, it represents a significant decrease in the efficacy of the treatment. Second, the NNT begins to rise exponentially once exceeding this threshold, and therefore the impact of further degrees of inactivity becomes more pronounced. This 10% increase could be a 10% incidence of B.1.351 circulating locally or a 20% incidence of some yet undefined mutation that decreases the efficacy of BAM-ETE by 50%. This cutoff point is dynamic and subject to change based on local supply of both products as well as variant rates nationally, which may lead to the need to prioritize CAS-IMD for a part of the country where problematic variant rates are higher. Additional considerations for

Table 2. Impact of Variant/Mutation Frequency Among Locally Circulating Viruses and Influence on Efficacy on NNT of Monoclonal Antibodies^a

Mutation Frequency, %	Not Treated Hospitalization Rate, %	Mutation Making mAbs Ineffective		Mutation Making mAbs 50% Less Effective		Mutation Making mAbs 25% Less Effective	
		mAb Treated Hospitalization Rate, %	NNT	mAb Treated Hospitalization Rate, %	NNT	mAb Treated Hospitalization Rate, %	NNT
0	7	2	20	2	20	2	20
10	7	2.5	22	2.25	21	2.13	21
20	7	3	25	2.5	22	2.25	21
30	7	3.5	29	2.75	24	2.38	22
40	7	4	33	3	25	2.5	22
50	7	4.5	40	3.25	27	2.63	23
60	7	5	50	3.5	29	2.75	24

Abbreviation: NNT, number needed to treat.

^aTo determine the impact of mutation frequency/effect on monoclonal antibodies, the following process was followed. The 5% absolute difference between treatment and no treatment was multiplied by the mutation frequency (eg, 0.1 for 10%) and the impact the mutation has on efficacy (eg, 0.5 for a 50% decrease in efficacy). The sum of these numbers was then subtracted from the 5% absolute difference to determine the new absolute difference (eg, $5 \times 0.1 \times 0.5 = 0.25$; $5 - 0.25 = 4.75$) and then subtracted from the untreated event rate to determine the new event rate for treated patients (eg, $7 - 4.75 = 2.25\%$). The new absolute difference was then used to calculate the NNT (eg, $100/4.75 = \text{NNT } 21$).

scenarios where supply cannot meet demand include prioritizing CAS-IMD for the highest-risk patients currently authorized under the EUA. A recent, real-world study of BAM found the highest hospitalization rate in untreated patients ≥ 65 years of age (19%), with an NNT of 8 to prevent a hospitalization in this subset of patients [8]. Given that percentage decreases in efficacy would impact more patients in this group, it would be sensible to treat these patients with CAS-IMD, while utilizing BAM-ETE in other patients. If infection rates and the severity of presentation continue to decrease in this population due to successful vaccination campaigns, prioritization could focus on other groups with the highest risk for poor outcomes such as the immunocompromised, morbidly obese, or minoritized patient populations.

Importantly, not all sites have the ability and/or resources to sequence all, or even some, of the viruses present locally. In this setting, it is reasonable to use publicly available statewide data to inform these decisions. This can be performed by downloading all statewide sequence data that are uploaded into GISAID, an open access database of viral sequences. The data downloaded from this website can then be uploaded into Nextclade, which translates sequencing data into amino acid substitutions to allow for the assessment of the frequency of key RBD mutations in statewide samples. The above processes for assessment of the impact of mutation rates on treatment options can then be applied to the statewide data set in order to inform monoclonal antibody treatment decisions. One important caveat to statewide surveillance data is that the sample of viruses sequenced can include a combination of routine surveillance and more targeted sequencing. As samples in these data sets will include outbreak investigations and targeted surveillance of high-risk populations for VOC, these data should be interpreted cautiously, as they may be less reflective of overall local epidemiology.

Regardless of the strategy chosen, it will be critical for monoclonal antibody programs to follow high-level outcomes within one's institution (event rate over time), emerging literature on the clinical efficacy of the various monoclonal antibodies against different mutations, available supplies of various products, and local and national changes in circulating virus to determine if the strategy needs to be modified. Furthermore, it will be critical that monoclonal antibody programs statewide and national policies and guidelines support processes to distribute products active against variant viruses to areas that are most impacted by these viruses and limit use of the monoclonal antibodies active against key RBD mutations to settings where they are needed.

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Patient consent. This analysis does not include factors necessitating patient consent.

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