UJEMI PERSPECTIVES

Evaluating the future of monoclonal antibody therapy for SARS-CoV-2

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SUMMARY A range of therapeutic options exist for those at high risk for developing severe coronavirus disease 2019 (COVID-19) infection. Monoclonal antibody (mAb) therapies and antiviral therapies are two major categories that have been relatively well-defined. However, few studies have directly compared these two forms of therapy. With the emergence of new variants of concern (VoCs), resistance to therapeutics has become an issue. The extensive mutations found on the Omicron variant has compromised many currently available neutralizing mAb therapies. Eli Lilly's Bebtelovimab was recently authorized in the United States, but its clinical success has yet to be proven. This article will highlight the current role of mAb therapy in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as well as its future use, focusing on 1) How does Bebtelovimab compare to other mAb therapies for SARS-CoV-2 and 2) What are the advantages and disadvantages of mAb therapy in comparison to antivirals for SARS-CoV-2? Answering these questions will help to strategize the development of novel therapeutic agents in targeting emerging VoCs in addition to investigating the benefits and limitations of each form of therapy. This article emphasizes the potential of Bebtelovimab as a broad-spectrum mAb while addressing the need to examine novel combination therapies targeting conserved epitopes in order to combat resistance. The comparison of mAbs to antivirals also exposes the challenge of manufacturing cost, drug supply, and distribution in the healthcare system, which has an impact on the long-term clinical feasibility and success of these therapeutics.

INTRODUCTION

The ongoing coronavirus disease 2019 (COVID-19) pandemic continues to pose significant challenges to global health. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has caused millions of deaths worldwide and remains a major area of research, especially in the development of therapeutics (1,2). Monoclonal antibody (mAb) therapy was one of the first forms of treatment to be developed for SARS-CoV-2 (2). The first mAb treatment that gained Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration (FDA) for SARS-CoV-2 was Eli Lilly's Bamlanivimab, in November 2020, four months after the antiviral Remdesivir by Gilead Sciences and one month before the Pfizer vaccine (3,4). Most mAbs for COVID-19 target the receptor binding domain (RBD) of the SARS-CoV-2 spike protein and work by preventing the virus from attaching to angiotensin-converting enzyme 2 (ACE2) and infecting cells (2). mAb therapies have shown success in preventing severe disease progression in non-hospitalized high-risk individuals (5).

Several variants of concern (VoCs) have emerged over the past couple years, including Alpha, Beta, Gamma, Delta, and the most recent Omicron variant, which currently dominates in several countries (1,6). Although Omicron is milder compared to previous variants such as Delta, its high transmissibility has led to surge of COVID-19 cases and risks severe illness in vulnerable populations, including those who are unvaccinated, immunocompromised, elderly, or suffering from comorbidities (6). Several previously authorized mAb therapies have been discontinued or limited due to resistant SARS-CoV-2 variants, including Eli Lilly's Bamlanivimab + Etesevimab and Regeneron's Casirivimab + Imdevimab (1,7). This was the

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case with the Omicron variant, whose spike protein contains over 30 mutations and half of those are in the RBD, which is the target site of many mAbs (7).

Before the authorization of Eli Lilly's most recent mAb Bebtelovimab in February 2022, GlaxoSmithKline and Vir Biotechnology's mAb Sotrovimab ran into limited supply as it was the only mAb that retained neutralization activity on the Omicron variant (8,9). While bebtelovimab is a promising mAb therapeutic, antiviral therapies such as Remdesivir and Pfizer's new oral pill Paxlovid also exist and are effective against Omicron (10). With the rise of new SARS-CoV-2 VoCs, there is a need to evaluate the efficacy of current mAbs and the role of mAb therapy among other therapeutic options.

PROPOSED RESEARCH QUESTIONS

There is a range of mAb and antiviral therapies available for the treatment of SARS-CoV-2 with reported efficacy against the Omicron variant. The recently authorized Bebtelovimab has shown encouraging neutralizing effects against Omicron, but with the potential emergence of new variants, it is important to evaluate Bebtelovimab's mechanism of action and how it compares to other mAb therapies. While there is a great extent of research on mAb and antiviral therapies, not many studies have compared the two types of therapy and there is limited understanding of the feasibility of implementing these strategies clinically. Therefore, this article will assess the efficacy of Bebtelovimab in comparison to other mAb therapies as well as review the advantages and disadvantages of mAb therapy in comparison to antivirals for SARS-CoV-2.

PROPOSED PROJECT NARRATIVE

How does Bebtelovimab compare to other mAb therapies for SARS-CoV-2? Given the range of mAb therapies that had originally received EUA for SARS-CoV-2 treatment and the fact that only a few remain efficacious against the Omicron variant (Table 1) (8,9,11,12), it is critical to compare and contrast each therapeutic to determine what gives certain ones an advantage over others. Bebtelovimab is the most recently authorized mAb and since it is so novel, there is a limited amount of clinical data that exists (8,9). Hence, it is imperative to understand its mechanism of action and efficacy against key VoCs in comparison to other mAb therapies.

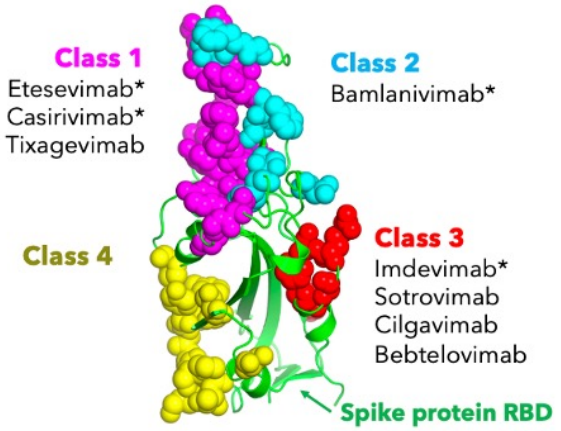
TABLE 1. Summary of authorized mAb therapies for SARS-CoV-2 in the US and Canada.

mAb Therapy	Source	EUA in US	Approved in Canada
*Bamlanivimab	Eli Lilly	Nov 9, 2020	Nov 20, 2020
*Casirivimab + Imdevimab	Regeneron	Nov 21, 2020	June 9, 2021
*Bamlanivimab + Etesevimab	Eli Lilly	Feb 9, 2021	(under review)
Sotrovimab	Vir Biotech	May 26, 2021	July 30, 2021
Tixagevimab + Cilgavimab (Evusheld)	AstraZeneca	Dec 8, 2021	(under review)
Bebtelovimab	Eli Lilly	Feb 11, 2022	(under review)

* = discontinued/limited due to resistant SARS-CoV-2 variants (information obtained from FDA and Health Canada)

In terms of binding mechanism to the virus, all authorized mAbs target the spike protein RBD of SARS-CoV-2, however, their specific binding epitopes vary (Figure 1) (2,13). Based on classification by Barnes et al., Class 1 antibodies bind the face of the ACE2 contact site only when the RBD is in the up configuration whereas Class 2 antibodies bind whether it is in up or down configuration (13-15). Class 3 antibodies bind the opposite side of the RBD, which has less overlap with ACE2 binding. Lastly, Class 4 antibodies target a site deep within the interior face of the spike protein and usually have poor neutralizing

activity (13-15). All antibodies that retain efficacy against Omicron participate in Class 3 binding, including Bebtelovimab (Figure 1).



mAb	Class
Bamlanivimab + Etesevimab*	2 + 1
Casirivimab + Imdevimab*	1 + 3
Sotrovimab	3
Tixagevimab + Cilgavimab	1 + 3
Bebtelovimab	3

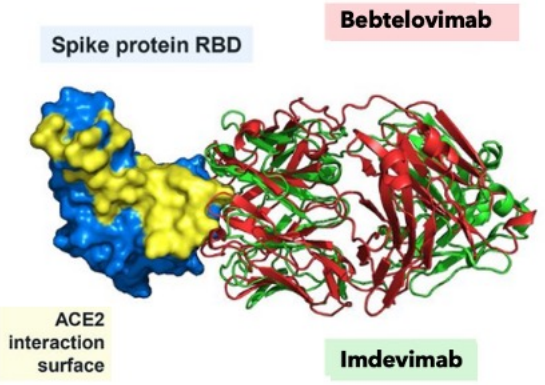
* = *Ineffective against Omicron*

(Figure adapted from Shrestha et al., 2021)

FIG. 1 Antibodies and their binding epitopes in the spike protein RBD of SARS-CoV-2. Class 1 antibodies are depicted in pink, Class 2 in blue, Class 3 in red, and Class 4 in yellow. There are no Class 4 mAbs currently authorized by the FDA. Table summarizes the authorized mAbs and their classification.

Interestingly, Bebtelovimab binds very similarly to Imdevimab (Figure 2) (16). Imdevimab is one of the two antibodies in the Regeneron cocktail, which does not neutralize Omicron (7). Both antibodies bind to a conserved region of the RBD that is not prone to mutations, except it was found that Bebtelovimab is more sequence divergent and has more contact surface area on the RBD compared to Imdevimab (16). Studies have also reported that Bebtelovimab retained broad-spectrum neutralization activity against all VoCs and was 60-fold more potent than Sotrovimab at neutralizing Omicron (8,16).

Overall, Bebtelovimab is a promising SARS-CoV-2 mAb therapy that may aid in relieving the supply shortage of Omicron neutralizing therapeutics. Although research has shown Bebtelovimab to be potent neutralizer of all VoCs, further therapeutic development and advancement is necessary to keep up with evolving SARS-CoV-2 mutations.



(Figure adapted from Westendorf et al., 2022)

FIG. 2 Structural overlay of Bebtelovimab and Imdevimab binding to the spike protein RBD of SARS-CoV-2. ACE2 interaction surface is shown in yellow on the blue spike protein RBD. Bebtelovimab is depicted in red and Imdevimab in green.

What are the advantages and disadvantages of mAb therapy in comparison to antivirals for SARS-CoV-2? Neutralizing mAbs and antivirals were both developed early on in the COVD-19 pandemic and were quickly authorized for clinical use (11,12,16). Although the benefits and limitations of each form of therapy have been discussed, few studies have directly compared them to each other. It is important to investigate the similarities and differences between mAbs and direct-acting antivirals in order to identify their role within the pandemic, determine the feasibility of potential therapeutics, and discuss what the future of COVID-19 treatment may look like.

Both mAbs and antivirals have shown to reduce death and hospitalizations in patients at high risk for severe disease progression (18,19). However, these treatments must be given early on in the course of infection in order to be effective (19). Compared to antiviral therapy, mAbs for SARS-CoV-2 offer several advantages such as duration of effect and the availability of authorized options for disease prevention (20-24). mAb therapies have been reported to offer protection for up to a few months, whereas antivirals only circulate

throughout the bloodstream of patients for a few days, which is attributed to a shorter drug half-life (20-22). Furthermore, certain mAb therapies have been approved for pre- and post-exposure prophylaxis (23,24). Antivirals, such as Remdesivir and Paxlovid, have not yet been authorized for SARS-CoV-2 prevention (11).

As for disadvantages of mAb therapy, ease of administration and cost are factors of concern. mAbs must be administered by a health care provider through IV infusion or subcutaneous injection (25), whereas Paxlovid is a pill that can be easily self-administered by oral ingestion (26). In addition, the Regeneron's mAb therapy costs the US government $2100 per dose (27), which is almost 4 times more expensive than a course of Paxlovid antiviral pills, priced at $530 (28).

Overall, mAbs and antiviral therapies share similarities, but each have their strengths and weaknesses. Out of all the aspects discussed, the high manufacturing cost of mAbs appears to be a major limiting factor for this form of therapy. Receiving adequate government funding to support this therapy and access in developing countries may prove to be challenging. However, with the current shortage of drugs effective against Omicron and the evolving landscape of COVID-19 VoCs, it is still important to keep investigating both mAb and antiviral therapies.

POTENTIAL IMPACT/CONCLUSIONS

This article has discussed the current role of mAb therapy within the context of the COVID-19 pandemic, highlighting the recently approved Bebtelovimab and also evaluating neutralizing mAbs against other antiviral therapies.

Class 3 antibodies are of interest since the currently authorized mAbs that retain efficacy against Omicron all bind to the same conserved epitope region (13) (Figure 1). Minor differences at the sequence and structural level of mAb therapies can make a significant difference in neutralization activity as noted by the comparison of Bebtelovimab and Imdevimab (16). With the emergence of new VoCs, it is critical to continue developing novel strategies and therapeutics to combat resistance. All mAbs approved for use in the US and Canada act on the RBD (2). It may be important to consider antibodies that bind regions other than the RBD, such as the N-terminal domain, which has been of interest in several studies, including one that experimented with a combination of RBD and N-terminal domain mAbs (29,30).

There is growing interest in the use of combination therapy to combat the rapid evolution of viral resistance, but there is limited research on the potential of combining neutralizing mAb therapy with antiviral therapy. As outlined in this article, mAbs and antivirals offer several advantages and disadvantages. Although both have played a significant role in preventing severe illness in high-risk individuals as well as decreasing hospitalization and mortality (18,19), differences in duration of effect, availability of treatment for preventative use, mode of administration, and cost were discussed. The biggest concern noted in regard to mAb therapy was its high cost, which may be a limiting factor in the development of combination therapies. With antiviral therapies such as Paxlovid being much cheaper and easier to administer, the question arises as to whether mAbs are a sustainable form of therapy for SARS-CoV-2. As the COVID-19 pandemic continues to evolve, there is a growing need to continue evaluating therapeutic options and prioritize the distribution of these therapies to those who need it.

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