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Efficacy and safety of bamlanivimab in patients with COVID-19: A systematic review and meta-analysis

Amani B *et al.* Bamlanivimab for COVID-19

Abstract

BACKGROUND

Monoclonal antibodies (mAbs) had shown clinical benefits against coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Several studies have been reported the use of bamlanivimab as a promising treatment option for COVID-19.

AIM

To synthesize the latest evidence for the efficacy and safety of bamlanivimab alone in the treatment of adult patients with COVID-19.

METHODS

A literature search was conducted in PubMed, Cochrane Library, Web of Science, medRxiv, and Google Scholar databases using “SARS-CoV-2”, “COVID-19”, “LY-CoV555”, and “Bamlanivimab” keywords up to January 25, 2023. The quality of included studies was assessed using the Cochrane bias tools. The Comprehensive Meta-Analysis software version 3.0 was used to analyze the data.

RESULTS

A total of 30 studies involving 47368 patients were included. A significant difference was observed between the bamlanivimab and standard of care/placebo groups in terms of mortality rate [risk ratio (RR) = 0.44, 95% confidence interval (CI): 0.30-0.64] and hospitalization rate (RR = 0.51; 95%CI: 0.39-0.68); while the two groups exhibited no significant difference in terms of intensive care unit (ICU) admission and emergency department (ED) visits ($P > 0.05$). Compared to other mAbs, bamlanivimab was associated with higher rate of hospitalization (RR = 1.44; 95%CI: 1.07-1.94). However, no significant difference was detected between the bamlanivimab and other mAbs in terms of mortality rate, ICU admission, and ED ($P > 0.05$). The incidence of any adverse events was similar between the bamlanivimab and control groups ($P > 0.05$).

CONCLUSION

Although the results suggest the efficacy and safety of bamlanivimab in COVID-19 patients, further research is required to confirm the efficacy of this drug for the current circulating SARS-CoV-2 variants.

Key Words: SARS-CoV-2; COVID-19; Bamlanivimab; Monoclonal antibody

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Core Tip: The present study is the most comprehensive systematic review and meta-analysis on the efficacy and safety of bamlanivimab in the treatment of coronavirus disease 2019 (COVID-19). A significant difference was observed between the bamlanivimab and standard of care/placebo groups in terms of mortality rate and hospitalization rate. while the two groups exhibited no significant difference in terms of intensive care unit admission and emergency department visits. The present results suggested that bamlanivimab might be effective and safe for the treatment of COVID-19.

INTRODUCTION

Despite a high rate of vaccination, cases of breakthrough coronavirus disease 2019 (COVID-19) have been reported worldwide^[1]. Consequently, numerous pharmaceutical interventions have been proposed to prevent and manage severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the primary cause of COVID-19^[2]. Numerous clinical studies have demonstrated that various monoclonal antibodies (mAbs), including sotrovimab^[3], casirivimab/imdevimab^[3,4], cilgavimab/tixagevimab^[5], regdanvimab^[6], bamlanivimab/etesevimab^[7], and bamlanivimab^[8] could be potentially

effective in reducing mortality and morbidity in patients with mild to moderate COVID-19. These interventions specifically target the spike protein of the SARS-CoV-2 virus, thereby inhibiting its activity^[9]. In particular, bamlanivimab has been approved by the United States Food and Drug Administration (FDA) for the treatment of nonhospitalized patients with mild to moderate COVID-19^[10]. It is worth noting that the FDA has recently revoked the authorization of bamlanivimab for the treatment of COVID-19 due to the emergence of SARS-CoV-2 variants that are resistant to this particular mAbs^[11]. However, bamlanivimab is still used in combination with etesevimab for the management of mild to moderate COVID-19 in individuals at high risk of developing severe symptoms^[12]. Multiple studies have shown that the administration of bamlanivimab is strongly associated with a notable decrease in the risk of mortality, lower hospitalization rates, and a decreased likelihood of intensive care unit (ICU) admission compared to treatment options that do not include mAbs^[8,13,14]. However, the effectiveness of anti-SARS-CoV-2 mAb agents against the Omicron variant of the virus has some concerns^[15]. Therefore, the objective of this study is to compile and analyze the available evidence regarding the effectiveness and safety of bamlanivimab in the treatment of patients with COVID-19.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses was utilized as a reporting guideline for conducting this systematic review and meta-analysis of primary studies^[16].

Literature search

An extensive literature search was conducted to gather relevant evidence. The search was performed in PubMed, Cochrane Library, Web of Science, medRxiv, and Google Scholar, up to January 25, 2023. Apart from the database search, the reference lists of the included studies were also examined to identify any additional relevant records. No language restrictions were applied. The search strategy in PubMed included keywords

such as “Coronavirus”, “COVID-19”, “SARS-CoV-2”, “Bamlanivimab”, and “LY-CoV555”. The specific search strategy in PubMed was as follows: (((((((Coronavirus[Title/Abstract]) OR (Coronavirus[MeSH Terms])) OR (COVID-19 [Title/Abstract])) OR (SARS-CoV-2 [Title/Abstract])) OR (COVID-19[MeSH Terms])) OR (SARS-CoV-2 [MeSH Terms])) OR (2019 novel coronavirus infection[Title/Abstract])) OR (2019-nCoV infection[Title/Abstract])) AND ((Bamlanivimab [Title/Abstract] OR (LY-CoV555 [Title/Abstract])).

Selection study

To be included in the study, the selected studies had to meet the following criteria: (1) Addressing adult patients who with positive COVID-19 results based on the polymerase chain reaction test; (2) Bamlanivimab alone as treatment; (3) Using placebo (PBO), standard of care (SOC), and other therapeutic interventions as the control group; and (4) Addressing mortality rate, hospitalization rate, emergency department (ED) visits, ICU admission rate, and incidence of adverse events as the measures of efficacy and safety. Animal studies, case reports, letter to the editor, and studies that did not report relevant outcomes were excluded from the analysis.

Risk of bias assessment

Two authors independently assessed the bias risk in observational studies and randomized controlled trials (RCTs) using Nonrandomized Studies of Interventions (ROBINS-I) tool and Cochrane Risk of Bias (ROB) tool, respectively^[17,18].

Data extraction

Two authors independently extracted the following data from the included studies: (1) Study characteristics including information such as the name of the first author, year of publication, location of the study, and study design; (2) Participant characteristics such as sample size, gender distribution, and the mean age of the participants; (3) Intervention and control including details on the sample size of both intervention and

control groups, and the treatment dosage and duration; and (4) Efficacy and safety outcomes consisted of the reported efficacy (*i.e.*, mortality rate, hospitalization rate, ED visits, ICU admission rate, and the incidence of adverse events). By independently extracting this data, the authors ensured a thorough and accurate collection of information for analysis.

Data analysis

The Comprehensive Meta-Analysis software was employed to compare the efficacy and safety between bamlanivimab and the control groups. The risk ratio (RR), along with a 95% confidence interval (CI), was employed to analyze the dichotomous variables. The level of heterogeneity was assessed using the I^2 statistic, with a value greater than 50% or a P -value less than 0.1, indicating high heterogeneity ($I^2 > 50\%$ or $P < 0.1$). A random-effects model was employed in highly heterogeneous studies, while a fixed-effects model was used for studies with low heterogeneity. Both RCTs and observational studies were analyzed together to estimate the effect size. Subgroup analyses were conducted based on age of patients (less than 65 years or 65 and over), sample size, and study design. Moreover, a sensitivity analysis was performed by excluding studies with remarkable risk of bias for outcomes of mortality rate and hospitalization rate. Publication bias was assessed by Begg's test and Egger's test.

RESULTS

Figure 1 depicts the study selection process, starting from the initial literature search, removal of duplicates, and screening based on ⁴ title, abstract, and full-text. Out of the initial 584 studies identified after removing duplicates, 49 full-text studies were considered for eligibility assessment. Ultimately, a total of 30 studies with 47368 patients were included in the meta-analysis^[8,10,11,13,14,19-43]. Excluded studies are presented in Figure 1 along with their corresponding reason. The majority of the included studies were of retrospective nature and conducted in the United States. Furthermore, most of the studies were published in 2021, coinciding with the SARS-

CoV-2 Delta wave. COVID-19 vaccination status was reported in a few numbers of studies. Studies mainly evaluated the efficacy of bamlanivimab in patients with mild-to-moderate COVID-19 infection. In most studies, bamlanivimab was administered at a dose of 700 mg. In some studies, however, patients received doses of 2800 and 7000 mg. More detailed information on the characteristics of the included studies is listed in Table 1.

Risk of bias assessment

Supplementary Tables 1 and 2 respectively show the risk of bias assessment determined by ROB and ROBINS-I tools. Accordingly, the included studies had acceptable quality.

Efficacy outcomes

Mortality rate: The pooled estimate revealed a significant difference in mortality rate of the bamlanivimab compared to the SOC/PBO groups (RR = 0.50; 95%CI: 0.36-0.70, $P < 0.05$, $I^2 = 15\%$) (Figure 2A). However, no significant difference was observed between bamlanivimab and other mAbs in terms of mortality rate (RR = 1.71; 95%CI: 0.85-3.44, $P = 0.12$, $I^2 = 0\%$) (Supplementary Figure 1).

Hospitalization rate: A significant difference was observed in the hospitalization rate of bamlanivimab-receiving patients compared to those treated with SOC/PBO (RR = 0.51; 95%CI: 0.39-0.68, $P < 0.05$, $I^2 = 80\%$) (Figure 2B). Moreover, a significant difference was detected between the hospitalization rate of the bamlanivimab group compared to mAbs one (RR = 1.44; 95%CI: 1.07-1.94, $P = 0.01$, $I^2 = 53\%$) (Supplementary Figure 2).

ED visits: The combined analysis of these studies revealed no significant difference in the frequency of ED visits between bamlanivimab-treated patients and those receiving SOC (RR = 0.69; 95%CI: 0.47-0.99, $P = 0.04$, $I^2 = 58\%$). No significant difference was observed between bamlanivimab and other mAbs in terms of mortality rate (RR = 0.96; 95%CI: 0.76-1.20, $P = 0.74$, $I^2 = 0\%$) (Figure 2C and Supplementary Figure 3).

ICU admission: The result of meta-analysis showed no significant difference in the ICU admission rate of the bamlanivimab-treated patients and those receiving SOC (RR = 0.82; 95%CI: 0.57-1.18, $P = 0.29$, $I^2 = 42\%$) (Figure 2D). Significant difference was observed between bamlanivimab and other mAbs in terms of ICU admission (RR = 1.60; 95%CI: 0.86-2.98, $P = 0.13$, $I^2 = 0\%$) (Supplementary Figure 4).

Safety outcomes

Any adverse events: The pooled estimate of included studies showed no significant difference between the bamlanivimab and SOC/PBO groups (RR = 1.01; 95%CI: 0.81-1.26, $P = 0.88$, $I^2 = 0\%$) (Figure 2E). Moreover, no significant difference was observed in adverse events between the bamlanivimab and other mAb groups (RR = 6.13; 95%CI: 0.71-52.72, $P = 0.09$, $I^2 = 1\%$) (Supplementary Figure 5).

Publication bias: No evidence of publication bias was detected for pooled estimate of mortality rate ($P = 0.24$) and hospitalization rate ($P = 0.11$) based on Begg test. However, Egger's test indicated a publication bias for pooled estimate of mortality rate ($P = 0.01$) and hospitalization rate ($P = 0.004$) (Supplementary Figures 6 and 7).

Subgroup and sensitivity analyses: The subgroup analysis showed no significance difference in mortality rate and hospitalization rate by mean age of patients treated with bamlanivimab compared to SOC/PBO and by sample size (Table 2). Sensitivity analysis also exhibited no significant change compared to the excluded studies (Table 2).

DISCUSSION

The objective of this study was to analyze and synthesize the most recent evidence on the effectiveness and safety of bamlanivimab, a mAb intervention, during the prevalence of the SARS-CoV-2 Omicron variant. Despite the protective role of vaccines against SARS-CoV-2 infection, effective treatments are still required to manage COVID-

19 disease, particularly with the emergence of new variants^[44]. The results demonstrated the efficacy of bamlanivimab in achieving positive clinical outcomes among patients diagnosed with COVID-19.

The results of the meta-analysis revealed a significantly lower mortality rate in the bamlanivimab-receiving individuals compared to those treated with SOC/PBO. However, this difference was not significant between the bamlanivimab and other mAb groups. Clinical studies showed the similar efficacy of mAb treatments in reducing COVID-19-induced death^[11,40]. Consistence to our findings, meta-analyses conducted on the efficacy of bamlanivimab revealed that treatment with bamlanivimab is significantly associated with a lower mortality rate compared to the control group^[45,46]. In general, the clinical evidence suggests that mAb treatments may contribute to a reduction in the mortality rate among patients with COVID-19^[4,30,34,42,47]. Targeting the spike protein of the SARS-CoV-2 virus with anti-SARS-CoV-2 mAbs may serve as a potential mechanism for reducing the mortality rate of COVID-19 patients^[48].

According to results of the present meta-analysis, bamlanivimab-treated patients had a lower likelihood of being admitted to the hospital compared to those receiving SOC/PBO. However, hospitalization rate was higher in the bamlanivimab group than the other mAbs group. Bamlanivimab treatment may contribute to a reduced rate of hospitalization among COVID-19 patients. Consistent with the mentioned finding, other meta-analyses^[45,46] on the efficacy of this drug also demonstrated that treatment with bamlanivimab is associated with a lower rate of hospitalization in patients with mild to moderate COVID-19 compared to control groups. This further supports the potential effectiveness of bamlanivimab in reducing the hospital admission in individuals with COVID-19. Indeed, real-world studies demonstrated that therapeutic mAbs, including bamlanivimab^[38,40], sotrovimab, casirivimab/imdevimab^[4,40], and bamlanivimab/etesevimab^[40] can significantly reduce the rate of COVID-19-related hospitalization. According to these studies, the use of these mAbs can effectively lower the severity of the disease and decrease the need for hospitalization in individuals affected by COVID-19.

The results of the present study did not demonstrate a significant positive effect of bamlanivimab on reducing the need for ED visits in patients with COVID-19 compared to the SOC/PBO or mAbs groups. However, a meta-analysis of RCTs comparing mAbs-receiving patients with PBO group indicated a significant association of mAbs with a lower rate of ED visits^[49]. A possible explanation to this difference could be due to difference in the type of mAb treatments as intervention or included study design.

According to the present meta-analysis, treatment with bamlanivimab was not significantly associated with lower rate of admission to ICU ward compared to SOC/PBO or mAbs. On the contrary, a meta-analysis by Xiang *et al*^[45] showed a significant association of bamlanivimab with reduced ICU admission rate compared to the controls. This difference can be due to the number of studies included in the quantitative analysis. Compared to Xiang *et al*^[45], the present research identified and included more studies in the meta-analysis of data on ICU admission rate.

Consistent with previously published meta-analyses^[45] on the safety profile of bamlanivimab, the present study found similar incidence of adverse events in both the bamlanivimab and control groups. In general, the bamlanivimab-related incidence of adverse events in COVID-19 patients was mild and well-tolerated^[11,19,39]. The most frequently adverse events in studies included nausea, diarrhea, headache, and respiratory distress^[21,29]. In terms of severe adverse events, no significant difference was observed between the bamlanivimab and control groups. Chen *et al*^[21] found no cases of discontinuations due to adverse events in bamlanivimab-treated patients at different doses (700, 2800, and 7000 mg). Gottlieb *et al*^[29] also found similar results in COVID-19 patients receiving bamlanivimab doses of 700, 2800, and 7000 mg.

Two important points should be considered in the interpretation of the present results. First, several studies have documented evidence of post COVID-19 condition among individuals after the initial SARS-CoV-2 infection which is a serious problem for many recovered COVID-19 patients^[50-52]. Given that post COVID-19 conditions are highly important to the design effective treatments for COVID-19 and due to lack of validated treatment for post COVID-19 condition, longitudinal monitoring of COVID-

19 patients is highly vital to develop the effective therapeutic agents^[52]. Second, studies have shown the resistance of some SARS-CoV-2 variants to bamlanivimab. Hoffmann *et al*^[53] reported the resistance of SARS-CoV-2 variant B.1.1.7 to bamlanivimab. Clinical studies by Peiffer-Smadja *et al*^[54] showed the emergence of resistance mutants in bamlanivimab-receiving COVID-19 patients. A RCT conducted by Choudhary *et al*^[55] reported the emergence of SARS-CoV-2 escape mutations in COVID-19 patients during treatment with bamlanivimab (700 mg). However, no resistance mutations were identified in patients treated with 7000 mg bamlanivimab. These findings highlight the importance of viral resistance during the development of treatments for COVID-19 patients. SARS-CoV-2 mutations may also lower the effectiveness of current preventive therapies in individuals, including vaccines. The SARS-CoV-2 variant B.1.351 could significantly reduce the efficacy of Novavax COVID-19 vaccine^[56].

The present study has some remarkable limitations. Firstly, the included studies did not report the type of SARS-CoV-2 variant. Therefore, the present findings may not be applicable to some SARS-CoV-2 variants of interest. Secondly, the majority of studies included in the meta-analysis were retrospective, causing an inherent risk of bias. Moreover, many of these retrospective studies did not utilize propensity score matching to minimize selection bias and confounding variables. Thirdly, we could not perform subgroup analyses based on these variables as the information on the comorbidity percentage and COVID-19 vaccine status of the studies was not complete. Therefore, the present results cannot be generalized to patients with unknown COVID-19 vaccine status. Finally, the present results should be interpreted with caution due to the presence of potential publication bias in several outcomes.

CONCLUSION

The present meta-analysis demonstrated the association of bamlanivimab treatment with a reduction in the mortality rate, hospitalization rate, and ED visits in patients with COVID-19 compared to SOC-receiving group. However, it did not show a significant efficacy in improving clinical outcomes compared to other mAb treatments.

In terms of safety, bamlanivimab was safe and well-tolerated in patients with COVID-19. However, studies did not report the specific type of SARS-CoV-2 variants. Therefore, the findings may not be directly applicable to patients with current SARS-CoV-2 variants. Future research should be focused on the efficacy of bamlanivimab against the current SARS-CoV-2 variants, especially in immunocompromised patients who are more susceptible to the new SARS-CoV-2 variants in terms of mutations and resistance to treatment with mAbs. Moreover, the comorbidity percentage and COVID-19 vaccination rate should be considered in evaluating the efficacy of bamlanivimab in COVID-19 patients.

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