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Do we need bamlanivimab? Is etesevimab a key to treating Covid-19?

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ABSTRACT

Introduction: Treatments for subjects with Covid-19 are required. One approach is neutralizing monoclonal antibodies. Bamlanivimab and etesevimab are monoclonal antibodies to SARS-CoV-2.

Areas Covered: This evaluation is of the phase 3 BLAZE-1 clinical trial, which was of bamlanivimab plus etesevimab in adult ambulatory participants with a risk factor for, and mild to moderate, Covid-19 illness. The primary outcome was Covid 19 related hospitalization of ≥ 24 hours or death from any cause by day 29, and this occurred in 2.1% subjects in the bamlanivimab/etesevimab group, compared to 7.0% in the placebo group.

Expert Opinion: In the pandemic, the attempts by the FDA to shorten approval processes for medicines and by journals to make information available in a timely manner are admirable. However, these shortened processes made negotiating the details of BLAZE-1 and producing accurate and critical appraisals difficult. It seems to me that if there are any benefits of bamlanivimab alone in Covid-19, they are not clear-cut. Bamlanivimab has limited effects against the beta and gamma variants and is not effective against the delta variant. Thus, the benefits of bamlanivimab/etesevimab in the phase 3 of the BLAZE-1 may be solely due to etesevimab, and this needs to be tested.

1. Introduction

This key paper evaluation is of bamlanivimab (LY3819253/LY-CoV555) plus etesevimab (LY3832479/LY-CoV016) for the treatment of ambulatory participants with mild or moderate Covid-19 in the phase 3 clinical trial of BLAZE-1: NCT04427501 [1]. By now, most people are familiar with the characteristics of Covid-19, the pandemic sweeping the world: difficulties in breathing, fatigue, fever, malaise, and loss of sense of smell, that can progress to acute respiratory distress syndrome and viral pneumonia. Death is most common in the older-aged, especially those with chronic medical conditions such as lung disease, cardiovascular disease, diabetes, obesity, and cancer.

Although vaccination is the obvious way to prevent Covid-19, it will still occur in subjects who have not been vaccinated and for those that the vaccine was ineffective in. Thus, treatments for subjects with Covid-19 are required. One approach is neutralizing monoclonal antibodies. Bamlanivimab and etesevimab are monoclonal antibodies to SARS-CoV-2.

SARS-CoV-2 enters cells after the binding of its spike protein to receptors for angiotensin-converting enzyme 2 (ACE2). Bamlanivimab is a monoclonal antibody that mimics LY-CoV555, an anti-spike neutralizing antibody, derived from a convalescing Covid-19 subject. In a rhesus macaque challenge model of SARS-CoV-2 infection, bamlanivimab reduced viral replication by 10^2–10^5 in bronchoalveolar lavage on day 1, 3 and 6, and limited the respiratory and clinical signs of the disease [2].

BLAZE-1 started as a phase 2 trial of bamlanivimab in 452 outpatients with mild or moderate Covid-19, who did not have to have a risk factor for Covid-19. The phase 2 trial used doses of 700, 2800, or 7000 mg, and showed that the 2800 mg dose was more effective than the other two doses at reducing viral load on day 7. By day 11, the Covid-19 viral load was also much reduced in the placebo group, such that there was no significant difference between the loads between groups. Fewer subjects in the bamlanivimab groups (1.6%) were hospitalized than in the placebo group (6.3%), but any significance of this was not given. The major reduction in symptoms in the placebo group by days 7–11 also made it difficult to determine whether bamlanivimab was effective in reducing symptoms. However, the phase 2 trial of BLAZE-1 did establish the safety of bamlanivimab in mild to moderate Covid-19 [3].

Based on the results of the BLAZE-1 phase 2 trial, the FDA issued an emergency use authorization (EUA) in November 2020, for bamlanivimab in the treatment of subjects with SARS-CoV-2 at risk of progressing to severe disease and/or hospitalization [4]. Subsequently, this EUA was revoked in April 2021, as bamlanivimab alone was not effective against the increasing resistant variants of SARS-CoV-2. However, the EUA for the combination of bamlanivimab and etesevimab remained [5].

Etesevimab is the monoclonal antibody that mimics Ly-CoV016, which was also isolated from a convalescing subject who had had Covid-19. Like bamlanivimab, etesevimab binds to the receptor for ACE2 on the spike protein of SARS-Cov2,

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but to a different epitope. Etesevimab reduced viral load in a Rhesus monkey model of Covid 19 [6]. Etesevimab alone has been shown to be safe in healthy adults [7] and to reduce viral load in a case study of a subject with the delta (B.1.617.2) of Covid-19 [8]. These human studies of etesevimab were published after the phase 2/3 BLAZE-1 clinical trial of bamlanivimab and etesevimab in combination.

The phase 2/3 BLAZE-1 clinical trial was a continuation of the phase 2 BLAZE-1 study with the addition of group taking the combination of bamlanivimab and etesevimab. In phase 2/3, 577 subjects with mild to moderate Covid-19 were randomized to either bamlanivimab (700, 2800, or 7000 mg) or bamlanivimab 2800 mg and etesevimab 2800 mg or placebo. The primary outcome was change in viral load compared to placebo at day 11, which was not significant with bamlanivimab alone but was reduced by the combination (−4.37 vs −3.8 for placebo group). Associated with this, there were small improvements in symptoms, but most of these were not significant. There was also a reduction in hospitalizations, which was not significant with bamlanivimab alone, and only of borderline significance with the combination (placebo, 5.8%; combination, 0.9%, P = 0.049) [9].

Post hoc analysis of the phase 2/3 BLAZE-1 clinical trial showed that in the 189 participants aged ≥65 years or with a BMI ≥ 35 kg/m^2, the rate of hospitalizations was significantly lower (P = 0.042) with bamlanivimab/etesevimab (0%, 0 of 31 participants) than with placebo (13.5%, 7/52). Viral load from baseline was only significantly reduced by bamlanivimab/etesevimab. Thus, viral load differences were not significantly different with bamlanivimab groups alone [9]. The next logical step was to investigate bamlanivimab/etesevimab further and this was done in the phase 3 study of BLAZE-1 [1] discussed in the next section.

2. Phase 3 of BLAZE-1

BLAZE-1 included a phase 3 randomized, double blinded clinical trial of bamlanivimab plus etesevimab versus placebo in subjects who had recently been diagnosed with mild or moderate Covid-19. The trial was performed in the USA and sponsored by Eli Lilly in collaboration with the developers of bamlanivimab (AbCellera Biologics) and etesevimab (Shanghai Junshi Bioscience).

To be enrolled, subjects had to have a risk factor for severe Covid-19 such as age ≥65 years of age, body mass index ≥35 kg/m^2, chronic kidney disease, diabetes, immunocompromised, cardiovascular disease, and/or chronic respiratory disease. However, subjects were excluded if they had peripheral oxygen saturation of ≤93%, a respiratory rate of ≤30 breaths/min, or heart rate of ≥125 beats/min.

The 1035 subjects enrolled had a mean age of 54 years with 31% being ≥65 years of age, 19% had a peripheral oxygen saturation of <96%, and the median BMI was 34 kg/m^2. There were four days from symptom onset to randomization to a single dose of bamlanivimab and etesevimab, 2800 mg of each given intravenously, or placebo over one hour.

The primary outcome was Covid 19 related hospitalization of ≥ 24 hours or death from any cause by day 29, and this

occurred in 11/518 (2.1%) subjects in the bamlanivimab/etesevimab group, compared to 36/517 (7.0%) in the placebo group (P < 0.001). None of the subjects receiving the combination died, compared to 10 (1.9%) in the placebo group (P value not given). The secondary composite outcome of hospitalization, an emergency department visit, or death occurred less often in treatment group (2.3%) than placebo group (7.2%, P < 0.001). Hospitalization was lower and shorter in the bamlanivimab/etesevimab group (2.1%, 7.3 days) than placebo group (6.4%, 11.2 days, P values not given).

The secondary outcomes also included the change in baseline in the SARS-CoV-2 viral load, which decreased in the placebo group, and to a greater extent in the bamlanivimab/etesevimab group on days 3, 5, 7, and 11 after randomization, but a P value was only given for day 7. On day 7, the percentage of subjects with a high viral load was lower in the bamlanivimab/etesevimab group (9.8%) than the placebo group (29.5%, P < 0.001).

Mild or moderate Covid-19 is defined as having the following symptoms: fever, cough, sore throat, malaise, headache, pain, gastrointestinal symptoms, and shortness of breath on exertion. These symptoms resolved one day earlier in the treatment than in the placebo group. However, the proportion of subjects who had sustained symptom resolution was similar in both groups on days 22–29.

The incidence of adverse effects was low and similar in the bamlanivimab/etesevimab (1.4%) and placebo (1.0%) groups.

In their discussion, the authors point out that the beta variant, first identified in South Africa, and the gamma variant, first identified in Brazil, were not identified in BLAZE-1. Both of these variants have in vitro resistance to several monoclonal antibodies including bamlanivimab and etesevimab. The limitations to the trial, given by the authors, are that most subjects were White (93%) and very few were young adults (12–17 years, 1.1%). The numbers with chronic kidney disease, cardiovascular disease, and chronic obstructive pulmonary disease were also low at 3.5%, 7.4%, and 8.2%, as were those with preexisting immunological conditions (1.5%) or those receiving immunosuppressive agents (4.9%) [1].

3. Expert opinion

3.1. Eligible and outcomes

To be enrolled in the phase 3 of the BLAZE-1 clinical trial, subjects had to have a risk factor for severe Covid-19. This had an obvious positive impact on the results compared to the previous BLAZE-1 trials. Thus, as although no participants in bamlanivimab/etesevimab group died, 10 subjects in the placebo group did and most had a risk factor: 4 were ≥65 years old, 5 had BMI ≥ 35 kg/m^2, and 8 had hypertension/cardiovascular disease. However, the report of the phase 3 BLAZE-1 clinical trial does not clarify how many of the ambulatory subjects with mild or moderate Covid-19 were eligible, i.e. the percentage with risk factors. Thus, it is difficult to gage which percentage of subjects with mild or moderate Covid-19, with or without risk factors, are likely to have the beneficial outcomes seen in the phase 3 of BLAZE-1. This is important as in the BLAZE-1 phase 2 and phase 2/3 to be enrolled, subjects

were not required to have a risk factor, and the benefits, if any, were less than in the phase 3 trial.

Phase 3 of BLAZE-1 does not report on the use of other medicines for the treatment of Covid-19 (e.g. dexamethasone, antibiotics) or of supplemental oxygen in the bamlanivimab/ etesevimab or placebo group. Thus, we do not know whether the use of these was similar or not in both groups. If the use of other medicines or of supplemental oxygen for Covid-19 was higher in bamlanivimab/etesevimab group, these could have contributed to the apparent beneficial outcomes in this group. Alternatively, a higher use of medicines/supplemental oxygen could have suggested that the prognosis was worse in the bamlanivimab/etesevimab group, which would be unexpected given that it was a randomized trial.

3.2. Difficult to understand some aspects of trial

In the pandemic, the attempts by the FDA to shorten approval processes for medicines and by journals to make information available in a timely manner are admirable. However, these shortened processes made negotiating the details of the phase 3 BLAZE-1 trial difficult for me. For example, the methods section of the paper describes the patients as 'ambulatory patients who were 12 to 17 years of age,' but results presented are for adults with a mean age of 54, and the discussion clarifies that 'only 1.1% of the patients were 12 to 17 years of age.' A second example is that in Table 1, the median days from symptom onset to randomization is 4 for both the treatment and placebo groups but is given as 40 for the total group.

In the published paper, the results of all statistical evaluations are not given. For instance, the P value for effect of bamlanivimab/etesevimab on viral load is given for day 7 (P < 0.001), but not for days 3, 5, and 11, where the reduction in comparison with placebo is much less. The P value for participants with a persistent high viral load in the combination group vs placebo is also given for day 7 (P < 0.001) but not for the other days.

The protocol provided as a supplement to the phase 3 BLAZE-1 trial, started as being for bamlanivimab alone in the phase 2 clinical trial, and then was amended on numerous dates in response to discussions with the FDA to a phase 2/3 clinical trial and then phase 3 with bamlanivimab and etesevimab. The amendments are listed as changes or removals, but a clean document with the amendments made is not provided. This made it difficult for me, as an experienced evaluator of clinical trials, to get a clear picture of the trial protocol, and may have also confused others.

3.3. Is bamlanivimab necessary or should we be using etesevimab alone?

In the phase 2 [3] and phase 2/3 trials [9] of BLAZE-1, bamlanivimab alone was shown to be safe in the treatment of Covid-19 but did not demonstrate a clear-cut benefit. Subsequently, bamlanivimab 7000 mg was tested against placebo, in the presence of remdesivir in hospitalized subjects with Covid-19 in ACTIV-3: Therapeutics for inpatients with COVID-19 (TICO): NCT04501978. In addition to remdesivir,

participants were allowed supplemental oxygen and glucocorticoids. This trial was stopped by the data and safety monitoring board for futility in October 2020, when there was no indication that bamlanivimab was altering the time to sustained recovery or time to hospital discharge. Many of those enrolled in ACTIV-3 did have a risk factor for Covid-19, as the median age was 61 years, 52% had a BMI of ≥30 kg/m², and 68% had a coexisting illness (49% hypertension, 29% diabetes) [10]. Thus, there is no evidence from BLAZE-1 or ACTIV-3 that bamlanivimab is effective in the treatment of Covid-19.

The human studies of etesevimab alone in healthy subjects and one subject with the delta variant were published after the BLAZE-1 phase 2/3 study of bamlanivimab and etesevimab in combination [3]. There are no clinical trials registered to determine the effects of etesevimab alone in phase 2 or 3. It seems to me that there is little or no evidence that bamlanivimab alone is necessary for the benefits observed in combination with etesevimab, and that the benefits of the combination may solely be due to the etesevimab, and etesevimab alone should be tested in a phase 3 clinical trial in subjects, with and without risk factors, in Covid-19.

3.4. Different strains and pause in distribution of bamlanivimab/etesevimab

Bamlanivimab was developed from antibodies to the original SARS-CoV-2 and is effective against the alpha variant (B.1.1.7). An emerging problem with using bamlanivimab to treat the alpha variant is that a case study has shown that treatment can lead to the development of a SARS-CoV-2 spike protein escape mutation Q493R, which is not responsive to bamlanivimab [11]. As Q493 is also crucial for the binding of etesevimab to the spike protein, the mutation is also resistant to etesevimab [11].

The beta (B.1.351) and gamma (P.1) variants of SARS-CoV-2 have mutations in K417N, E484K, and N501Y, which increase the binding of the spike protein to the ACE2 receptor [12] making them more infectious than the original SARS-Cov-2. Unfortunately, these variants are resistant to bamlanivimab and etesevimab [12]. As these variants accounted for >11% of the cases of Covid-19 in the USA, the distribution of bamlanivimab/etesevimab was paused in June 2021 in favor of two alternative monoclonal antibody therapies with EUAs, casirivimab and imdevimab combined (REGEN-COV) and sotrovimab, which are likely to be effective against the beta and gamma variants [13].

The delta variant is now the predominant strain of Covid-19 in the USA, UK, and most of Europe. Bamlanivimab is not effective against the delta variant (B.1617.2) [14]. Etesevimab loses some of its effectiveness against the alpha variant compared to the original SARS-CoV-2 but remains effective against the delta variant [14].

3.5. REGEN-COV and sotrovimab

REGEN-COV is a combination of casirivimab and imdevimab, which bind to different spike proteins of SAR-COV-2, to have neutralizing potency against all the present variants (alpha, beta, gamma, delta, and epsilon) [15]. REGEN-COV reduces

viral load and symptoms in outpatients with Covid-19 [15] and prevents symptomatic Covid-19 and asymptomatic SARS-CoV -2 infection in previously uninfected household contacts of infected subjects [16]. The European Medicines Agency approved REGEN-COV for the treatment of Covid-19 in subjects who do not require supplemental oxygen but are at high risk of progressing to severe Covid-19 [17]. Subsequently, REGEN-COV has also been issued at EUA from the FDA for the emergency use as post-exposure prophylaxis for Covid-19 in adult and pediatric subjects at high risk to severe Covid-19, including hospitalization or death [18].

Sotrovimab was derived from an antibody (S309) isolated from a subject who had recovered from Severe Acute Respiratory Syndrome (SARS), but does target the spike protein of Covid-19. It is presently in clinical trial for Covid-19 including a comparative clinical trial with bamlanivimab, bamlanivimab and etesevimab, and REGEN-COV; NCT04790786 [19].

4. Conclusions

If there are any benefits of bamlanivimab alone in Covid-19, they are not clear-cut from the BLAZE-1 series of clinical trials or ACTIV-3. Bamlanivimab has limited effects against the beta and gamma variants and is not effective against the delta variant. Thus, the benefits of bamlanivimab/etesevimab in the phase 3 BLAZE-1 clinical trial may be solely due to etesevimab, and this needs to be tested.

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Declaration of interests

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