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Original Article

Early Treatment with Bamlanivimab Alone does not Prevent COVID-19 Hospitalization and Its Post-Acute Sequelae. A Real Experience in Umbria, Italy.

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Abstract. ***Background and Objective:*** **The use of monoclonal antibodies to the SARS-Cov-2 spike protein for early treatment of COVID-19 disease is being evaluated, with only phase 2 studies available to date. The emergency authorization of bamlanivimab monotherapy was obtained in November 2020 by the FDA and in March 2021 by Italian agency AIFA. Its use was then revoked in April 2021 by both. This study reports the results of bamlanivimab utilization in monotherapy in Umbria (Italian region) to verify whether, in a population with multiple risk factors, comparable results to the phase 2 BLAZE1 trial had been obtained.**
Methods: **Between March and April 2021, a retrospective observational study was performed on patients treated with bamlanivimab. Demographic and clinical characteristics before and after infusion were evaluated. Moreover, a telephone interview was conducted about 30 days after the infusion to evaluate the overall course.**
Results: **All patients had an early infection (mean 4±1.73 days), almost all by alpha variant (97%). No adverse events to treatment were observed. Altogether within 30 days, the hospitalization rate was 20%, 15% for COVID-19 related pathologies, versus 4% at 11 days in the BLAZE1 phase 2 study. In addition, worsening of some symptoms observed at baseline such as asthenia (77 vs. 51.3%), shortness of breath (38 vs. 23%) was registered, as well as the onset of non-restorative sleep (41%).**
Conclusion: **The clinical outcome after bamlanivimab monotherapy was far below the expectation despite the patients had been infected by a theoretically sensitive viral variant.**

Keywords: Bamlanivimab; COVID-19 hospitalization; real experience; Umbria.

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Introduction. Bamlanivimab binds to SARS –CoV-2's spike protein and prevents viral attachment to human surface ACE2 receptors.[1] Preliminary analysis of treatment with bamlanivimab alone in human beings resulted in lower rates of COVID-19-related hospitalization within 29 days compared to treatment

with the placebo (1.6% vs. 6.3%), and a post-hoc analysis demonstrated that the subgroup high risk patients receiving bamlanivimab had a reduced rate of hospitalizations compared to those receiving the placebo (4.2% v 14.6%).[2]

Based on the preliminary Phase 2 study (BLAZE 1), in November 2020, the Food and Drug Administration (FDA) authorized the monoclonal antibody bamlanivimab (LY-CoV555, Lilly) as monotherapy for emergency use (EUA) in outpatients for treating mild to moderate coronavirus disease 2019 (COVID-19) in patients with positive results of direct SARS-CoV-2 viral testing, aged 12 or over, weighing at least 40 kg and at high risk of progression towards severe COVID-19 and/or hospitalization.[2-3]

On February 6, 2021, likewise in Italy, the drug was temporarily authorized for the treatment of COVID- 19 by a Health Ministry Decree similar to the FDA: the drug was to be given as soon as possible after a SARS-CoV-2 positive test result and within 10 days of COVID-19 symptom onset.

Afterward, on April 16, the FDA revoked its Emergency Use Authorization, based on its ongoing analysis of the sustained increase of SARS CoV-2 viral variants that were resistant and the risk of treatment failure.[4] Indeed, as of mid-March 2021, approximately 20% of isolates sequenced in the U.S. were reported as lineages expected to be resistant to bamlanivimab alone, increasing from approximately 5% in mid-January 2021.[4]

In the meantime, in Umbria, from January to March, several P.1 (gamma) viral variant clusters were seen,[5] the "fragile" population was being vaccinated, and in March, bamlanivimab was first available.

The aim of the study was to describe the clinical use of bamlanivimab in Umbria (Italy) and compare the outcome according to the time of early infusion (within 72 hours) vs. late (>72 hours).

Materials and Methods. This study, carried out from March and early April 2021, was retrospective observational. We describe the characteristics, clinical outcomes, and safety of patients reported by their general practitioners as recently infected, with mild/moderate COVID-19 and at high risk of developing severe disease according to AIFA criteria (**Table 1**) who were admitted to the Day Hospital of Infectious Diseases Clinic of Perugia, to the COVID Hospitals of Spoleto and Città di Castello, in order to receive a single 700 mg intravenous (IV) infusion of bamlanivimab alone. Demographic, medical history, main comorbidities, virological (nasopharyngeal swabs), vaccination, and clinical data were collected from the medical records, and we calculated the timeliness of the treatment (within 72 hours) from the onset of symptoms. Temperature, blood pressure, respiratory rate, and oxygen saturation (SpO2) in resting-state were measured before and one hour after the infusion of bamlanivimab. Around thirty days after the infusion, patients were interviewed about their health state, the presence of mild adverse effects, the date and results of subsequent nasopharyngeal swabs, and any changes in pre and post-treatment symptoms.

Table 1. AIFA criteria for patients eligible for monoclonal antibody therapy for COVD-19 included in the Ministerial Decree of 6 February 2021 (GU n.32 of 8-2-2021).

Selection criteria for patients eligible for monoclonal antibody therapy for COVD-19 included in the Ministerial Decree of 6 February 2021 (GU n.32 of 8-2-2021)
• BMI≥ 35
• Subjects chronically undergoing peritoneal dialysis or hemodialysis
• Uncontrolled diabetes mellitus (HbA1c> 9.0% 75 mmol / mol) or with chronic complications
• Primary immunodeficiencies
• Secondary immunodeficiencies with particular regard to onco-haematological patients in treatment with myelo / immunosuppressive drugs, myelosuppressive drugs or less than 6 months from the suspension of treatment
• ≥ 65 years (in this case there must be at least one additional risk factor)
• ≥55 years with: - cardio-cerebrovascular disease (including hypertension with concomitant damage organ) - COPD and / or other chronic respiratory diseases (people with pulmonary fibrosis or needing O2 therapy for reasons other than SARS-CoV-2)
12-17 years with: • BMI ≥ 85th percentile for age and gender; • sickle cell anemia; • congenital or acquired heart disease; • neurodevelopmental disease, • dependence on technological device (e.g. subjects with tracheostomy, gastrostomy, etc); • asthma, or other respiratory diseases that require daily medications for them control
Persons hospitalized for COVID-19, or who receive oxygen therapy for COVID-19 are excluded

Table 2. Demographic, clinic and laboratory characteristics of total patients.

	Total Population
No. (%).	39
Age, mean (SD) [range], years	63.2 (15.8) [16-92]
Sex: Male, No. (%)	 20 (51.3)
Body mass index (BMI), Kg/m^2 mean (SD) [range]	29.2 (6.8) [17-54]
Comorbidities, No. (%)	
BMI ≥35 kg/m^2	15 (38.5)
Chronically undergoing peritoneal dialysis or hemodialysis,	10 (25.6)
Uncontrolled diabetes mellitus (HbA1c ≥9%) or with chronic complications	13 (33.3)
Secondary immunodeficiency (onco-haematological patient,immunosuppressive treatment)	11 (28.2)
Cardio-cerebrovascular disease (arterial hypertension with organ damage)	20 (51.3)
COPD and/or other chronic respiratory disease (pulmonary fibrosis or needing O2-therapy)	15 (38.5)
Primary immunodeficiency	10 (25.6)
Congenital or acquired heart disease	10 (25.6)
Neurodevelopmental disease	10 (25.6)
Vital Signs, mean (SD) [range]	
Temperature,°C, mean (SD) [range]	36.7 (0.77) [35-38.2]
Heart rate/min, mean (SD) [range]	81.3 (12.5) [58-110]
Respiratory rate/min, mean (SD) [range]	18 (2.9) [14-26]
Systolic blood pressure, mm/Hg , mean (SD) [range]	125 (15.6) [86-165]
Diastolic blood pressure, mm/Hg, mean (SD) [range]	75.3 (9.9) [47-100]
Oxygen saturation, % mean (SD) [range]	96.5 (1.9) [89-99]
Vaccination No. (%) 2 doses 1 dose	4/39 (10.2) 2/4 2/4
Genes detected No. (%)	
N	38/39 (97.4)
S	1/39 (2.5)
E	29/39 (74.39
Days from symptom' s onset to treatment, mean (SD) [range]	4.23 (1.73) [1-8]

Statistical Analysis. Standard descriptive statistics were used to summarize data, such as mean, standard deviation (S.D.), and percentage. Pearson Chi-square test was used to test differences between categorical variables. A p-value < 0.05 was considered for statistical significance. The student t-test for paired samples was used to test differences between continuous variables. SPSS statistical package release 24.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses.

Results. A total of 39 patients received the infusion of bamlanivimab: 51.3% were male, the mean age was 63±15.8 years (range 16-92), and cardiovascular disease was the main risk factor (51.3%). Fever (Temperature ≥ 37.5 °C) was present in 18 patients, and the most represented COVID-19 related symptoms were: cough (59%), myalgia (53.8%), and asthenia (51.3%). In addition, genes N, S, and E were detected in 38/39, 1/39, and 29/39 patients, respectively, by a reverse-transcriptase–polymerase-chain-reaction assay. (**Table 2**).

Four patients had been vaccinated (3 Pfizer, 1 AstraZeneca): 2 patients had received two doses (Pfizer), 2 only one (1 Pfizer and 1 AstraZeneca). In patients who had completed the vaccination, COVID-19 arose > 15 days after the second dose, while in the patient who had received only one dose of Pfizer, the disease arose after 8 days, and in the other who had taken AstraZeneca after 2 days. In the latter, the aggravation of an already known thrombocytopenia led to the patient's hospitalization.

The average time between the onset of symptoms and treatment was 4.23±1.73 days (range 1-8).

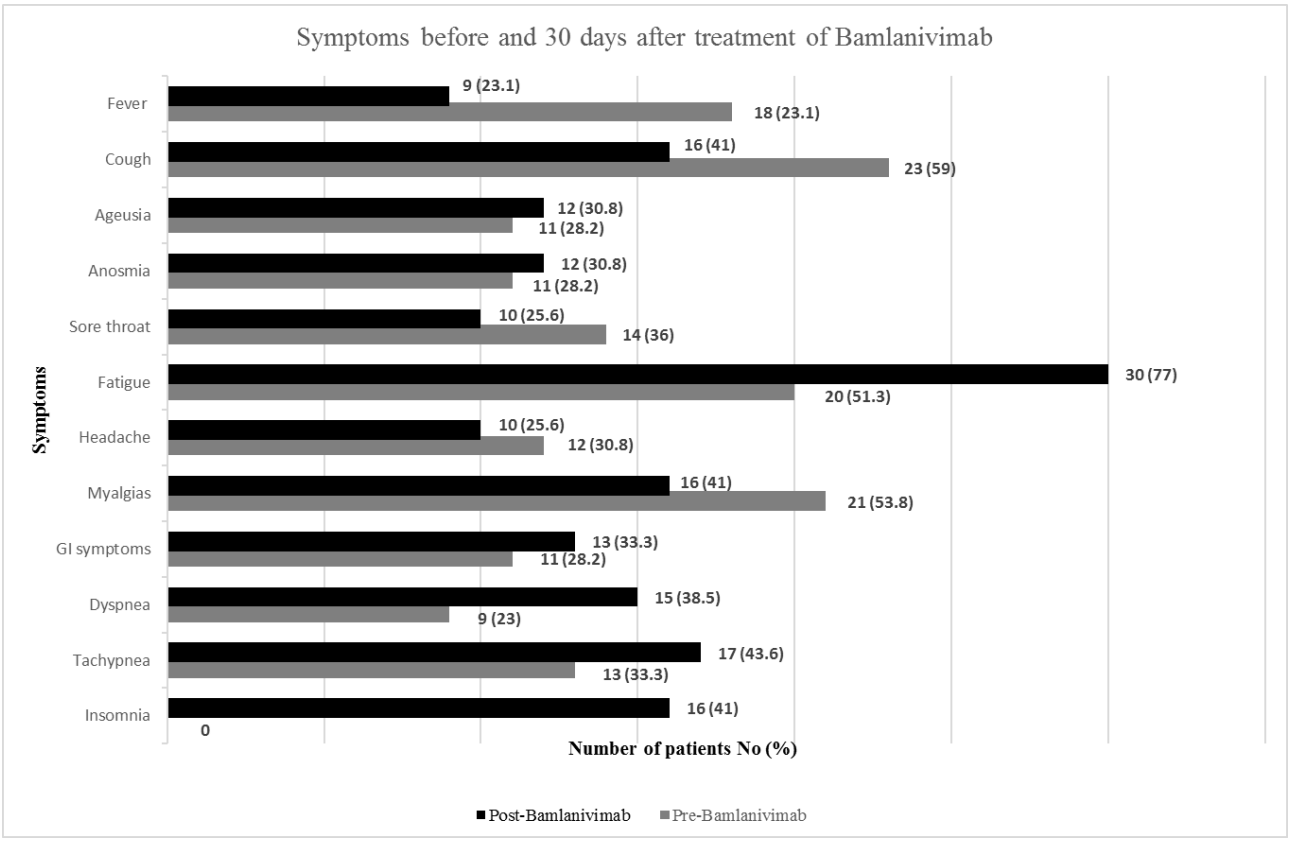

Figure 1. Symptoms before and 30 days after Bamlanivimab treatment.

Up to one hour after the bamlanivimab infusion, vital signs remained stable, and the patients were discharged in good health. No adverse events were documented in the following days.

Eight patients were hospitalized (one of them had received the first dose of AstraZeneca): 4 for COVID-19 pneumonia, 4 for the worsening of underlying diseases (thrombocytopenia, diabetic ketoacidosis, acute renal failure in chronic kidney disease, bacterial pneumonia). The hospitalization rate for any reason was 20 %, for COVID-19 pneumoniae, 10%

Thirty days after the infusion, patients reported an increase in symptoms such as asthenia (77 vs. 51%), dyspnea (38.5 vs. 23 %), tachypnea (44 vs. 33.3%) compared to baseline, and in 41% of the patients, the onset of a new symptom: insomnia (**Figure 1**).

The comparison between patients treated early (within 3 days) vs. later showed no differences regarding COVID-19 pneumonia hospitalization (3/15 vs. 2/24 p=0.289) or the nasopharyngeal swabs time negativization (mean 16.58±4.10 vs. 16.70±4.63 days p=0.942).

Discussion. The study reports on the clinical use of Bamanivimab in Umbria (Italy), which has to be read in a specific clinical context. An early treatment within 72 hours was obtained in 38.8% of cases; the mean time between the onset of symptoms and drug infusion was 4.23±1.73 days. Indeed, the cycle threshold (Ct) of the reverse-transcriptase–polymerase-chain-reaction assay was compatible with an early onset: moreover, 38/39 (97%) did not express gene S (alpha variant). The hospitalization rate was higher than expected; 20% of our patients were hospitalized within 30 days with no differences between early or late therapy. The number of hospitalizations for SARS-Cov-2 infection and related complications was 6 (15%). Pneumonia occurred in four patients with normal SpO2 at the time of bamlanivimab infusion.

Bamlanivimab, a monoclonal antibody directed against a spike protein epitope of SARS-Cov-2 and proposed for the treatment of COVID-19, was authorized as monotherapy for emergency use (EUA) in November 2020 by the FDA to treat outpatients with mild to moderate COVID-19 at high risk of progression and/or hospitalization. It was based on an interim analysis of the Phase 2 study BLAZE 1, concerning patients randomized in the United States from June 17 to August 17, 2020: it regarded 143 controls and 309 treated outpatients subdivided into three subgroups according to different doses of intravenous infusion (iv) bamlanivimab (700, 2800, and 7000 mg).[2] Subsequently, the BLAZE 1 study from August 22 to September 3 randomized another 114 patients who underwent the iv combination therapy bamlanivimab-etesevimab.[6] The whole trial was performed even before the diffusion of the several different variants that, to date, are affecting the whole world.[7]

Therefore, the final analysis concerned outpatients who had been randomized to receive a single infusion of

bamlanivimab alone (700 mg [n = 101], 2800 mg [n = 107], or 7000 mg [n = 101]), the combination treatment (2800 mg of bamlanivimab and 2800mg of etesevimab [n = 112]), or the placebo (n = 156).[6]

The inclusion criteria of the above trials were the presence of at least one mild or moderate symptom of COVID-19, the primary outcome was the change from base of the SARS-CoV-2 viral load at 11 days and, in the overall context of the secondary outcomes, the rate of hospitalizations within 4 weeks.

About 67% of patients had at least one risk factor for severe COVID-19 (aged ≥ 55 years, BMI ≥ 30, or ≥ 1 relevant comorbidity such as hypertension), and treatment was started early (median 4 days from onset of symptoms).

Compared with the placebo, there were no significant differences in the viral load change at 11 days with the three different doses of bamlanivimab alone. In contrast, the combination bamlanivimab - etesevimab significantly decreased SARS-CoV-2 log viral load at day 11 compared to the placebo (between-group difference, –0.57 [95%CI, –1.00 to –0.14], P = .01).

The hospitalization rate at 29 days was 1.0% in the 700 mg group and 0.9% in the combination therapy group, 5.8% in the placebo group.[6] Thus, the difference from the placebo was significant for the combination group (p=0.04), not for the 700 mg group (p=0.09). However, in a post hoc analysis, only 143 subjects were over 65 years old or with a BMI ≥ 35 (95 treated, 48 controls). Their hospitalization rate was 2.7% in the 700 mg group, 0% in the combination therapy group, 13.5% in the placebo group. Disease-related symptoms were monitored for the first 11 days, and the total symptoms score was assessed: an improvement for all the treated patient groups was observed.

Our case history refers to the use of bamlanivimab alone 700 mg iv from March 16 to April 16, until the FDA revocation of EUA. Therefore, the results of our experience must be contextualized to the local epidemiology where a wide diffusion of the English variant (alpha), which was not widespread at the time of the BLAZE 1 study, was being observed and where, in Umbria, outbreaks of variant P.1, (the Brazilian variant gamma), had first been observed two months before.

The entry criteria were different compared to BLAZE 1. Our case series consisted of patients who met the AIFA criteria for enrollment, apart from mild to moderate symptoms, which included in addition to BMI and age, other risk factors for potential disease progression such as: *chronically undergoing peritoneal dialysis or hemodialysis, secondary immunodeficiency, cardio-cerebrovascular disease* and so on (**Table 1**). Furthermore, 33% of the patients had more than one risk factor, while 18% had a BMI ≤ 35, and 15.4 % were ≤ 65 years old. Instead, BLAZE 1 entry criteria were only mild to moderate symptoms, without other risk factors.

The hospitalization rate was much greater than that observed in BLAZE 1, even considering the post hoc analysis of study BLAZE 1 where, introducing the age limit and a BMI >35, the rate of hospitalization of the controls more than doubled (13.5%). However, our cases appeared to be even more severe, having to consider the AIFA authorization criteria.

Our follow-up was 30 days, and we were able to document an average negative time of the nasopharyngeal swab of about 16.6 days.

However, in the face of virological response, a worsening of some baseline symptoms was seen: asthenia (77 vs. 51%), dyspnea (38 vs. 23%), tachypnea (44 vs. 33%), and in 41% of patients, the onset of a new symptom: a non-restorative sleep, thus configuring an evolution towards a sub-acute form of COVID -19.[8]

Limitations of our study were the small number of subjects and the absence of a control group. A control group of patients with the same characteristics (comorbidities) as those treated would have required a comparative clinical trial. In addition, the patients we treated were being followed by their general practitioners and only referred because they met AIFA criteria for monoclonal treatment (**Table 1**). Moreover, a control group would have needed randomization by general practitioners and was not ethical once an authorization procedure had been approved.

Conclusions. Despite several recent outbreaks of the gamma variant in Umbria, bamlanivimab in monotherapy was taken by patients largely infected by the alpha variant that seems to be susceptible to bamlanivimab,[9] missing E484K and L452R mutations which lead to resistance.[4]

However, the clinical and virological outcome observed in the epidemiological context was largely below the expected one of the phase 2 trial BLAZE 1, which had permitted its emergency use until April 2020, with a lower virological efficacy monotherapy compared to the combination was demonstrated. Furthermore, in a contemporary clinical setting with several SARS-CoV2 variants, the bamlanivimab monotherapy was safe. However, the hospitalization rate was 20%, much greater than that observed on the registrative trial BLAZE 1. Therefore, our results are in line with the grounds for withdrawing the use of bamlanivimab alone; the association of monoclonal antibodies in clinical practice context needs to confirm the expected antiviral efficacy.

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