



Original Article

**Pre and Post-Monoclonal Infusion Neutralizing Activity in a Subgroup of Patients Treated in the Presence of two SARS-CoV-2 Dominant Variant of Concern (VOCs) and an Ongoing Vaccination. Overall Clinical Efficacy of Two Monoclonal Antibodies Association in Umbria**

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**Abstract. Background and Objective:** In patients with mild-to-moderate COVID-19 and at high risk of progression, casirivimab/imdevimab and bamlanivimab/etesivimab were utilized in Umbria from late April to November 2021. This period was characterized by an initial prevalence of alpha (B.1.1.7) and its progressive substitution with the delta variant (B.1.617.2). Many delta infections occurred in patients already recently vaccinated.

Our study aimed to observe the clinical outcome of patients treated with mAbs associations in a subgroup in which viral isolation was obtained, the pre and post-infusion neutralizing antibody activity against their viral isolate.

**Methods:** In this retrospective observational study, the clinical outcome before and 30 days after infusion, the baseline neutralizing activity of sera against their viral isolate, and the titers of neutralizing antibodies (NAbTs) one-hour post-infusion relative to the type of mAbs associations were evaluated.

**Results:** Better efficacy of the mAbs combinations relative to monotherapy regarding global hospitalization ( $p = 0.021$ ) and 30 days symptoms ( $p < 0.001$ ) were seen. Infections after vaccination mostly occurred in the absence of neutralizing antibody titers (NAbT). SARS-CoV-2 delta variants were isolated within 2-4 months from vaccinations without NAbTs, or in the presence of high specific neutralizing activity after 5-6 months. NAbTs were higher after casirivimab/imdevimab infusion ( $p = 0.001$ ).

**Conclusions:** Alpha infections occurred prevalently in unvaccinated patients or after 5-6 months, while delta infections prevailed in vaccinated ones. A poor neutralizing activity in most of these patients was seen. A higher NAbT after infusion of casirivimab/imdevimab was observed.

**Keywords:** COVID19; mAbs; VOCs; Neutralizing activity.

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**Introduction.** The development of therapeutic monoclonal antibodies (mAbs) is currently at the forefront of fighting COVID-19 infection.

Most mAbs with activity against SARS-CoV-2 bind to the S1 subunit with their FAb domain and show their neutralizing activity, inhibiting virus engagement to the cell surface receptor ACE2.<sup>1</sup>

In November 2020 and in February 2021 US Food and Drug Administration (FDA) authorized the monoclonal antibody bamlanivimab as monotherapy<sup>2</sup> and casirivimab/imdevimab<sup>3</sup> and bamlanivimab /etesevimab<sup>4</sup> for emergency use in outpatients affecting a mild to moderate coronavirus disease (COVID 19) and at high risk of progression towards severe COVID-19 and/or hospitalization.

The emergency authorization was based on clinical trials in 2021,<sup>5,6</sup> which had been performed using neutralizing mAbs developed from convalescent COVID-19 patients infected by viral variants of SARS-CoV-2 before the emergence of the new SARS-CoV-2 Variants of Concern (VoC) alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2) which have been associated with ever greater transmissibility, altered virulence, or the ability to escape natural infection and vaccine-mediated immunity or current diagnostic tests.<sup>7</sup>

Indeed, on April 16, 2021, the FDA revoked the emergency use of bamlanivimab alone based on the increase of SARS-CoV-2 variants that were resistant to it.<sup>8</sup>

Few studies have reported the effectiveness of combinations of mAbs: Falcone M. et al. in patients infected by alpha and gamma SARS-CoV-2 variants receiving combinations of bamlanivimab /etesevimab or casirivimab/ imdevimab<sup>9</sup> observed that bamlanivimab/etesevimab should be used with caution in gamma variants because of a high risk of disease progression.

In our recent retrospective observational study, carried out from March to early April 2021, we found a clinical and virological outcome largely below the expected one of the phase 2 BLAZE 1 with bamlanivimab monotherapy,<sup>5</sup> both in the hospitalization rate and the improvement of 30-day symptoms.<sup>10</sup>

The aim of this study was to evaluate the efficacy of early administration of the combination of bamlanivimab /etesevimab or casirivimab/ imdevimab in outpatients infected by different SARS-CoV-2 viral variants with mild to moderate COVID-19 and at high risk to progression, in reducing the global hospitalization rate, the COVID19 pneumonia hospitalization and clinical symptoms after 30 days from therapy, in Umbria. Moreover, in Perugia-treated patients, we evaluated the

pre and post infusion neutralizing antibody titer (NAbT) towards their own viral isolate to highlight any different efficacy of the two combinations. The primary outcome was to evaluate any differences in the effectiveness of the two monoclonal combinations on their neutralizing capacity in the post-infusion sera of patients from Perugia in relation to VOCs. Secondary outcomes were the evaluation of the whole hospitalization rate, the COVID19 pneumonia hospitalization, and clinical symptoms after 30 days of therapy relative to bamlanivimab monotherapy.

**Materials and Methods.** This prospective observational study was carried out from April to November 2021. We describe the characteristics, clinical outcomes, and comorbidities of patients reported by their general practitioners according to AIFA criteria who were admitted to the Day Hospital of Infectious Diseases Clinic of Perugia and the COVID Hospital of Spoleto to receive a single 2100 mg intravenous (IV) infusion of bamlanivimab/etesivimab or 1200 mg casirivimab /etesivimab. Demographic, medical history, main comorbidities, vaccination, and clinical data were collected from the medical records. Moreover, we evaluated all patients' symptoms presented at admission. And at thirty days after the infusion.

Furthermore, at Infectious Diseases Clinic in Perugia, before the infusion of mAbs, we took a nasopharyngeal swab for virus isolation and routine blood samples for laboratory analyses and neutralizing antibodies' activity.

Temperature, blood pressure, respiratory rate, and oxygen saturation (SpO<sub>2</sub>) in resting-state were measured before and one hour after the infusion of mAbs.

We also calculated the timeliness of the treatment (within 72 hours) from the onset of symptoms.

Thirty days after the infusion, patients were called and 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.

Moreover, in Perugia, we cultured the virus from the patients' nasopharyngeal swabs in VERO E6 cells, as previously described.<sup>11</sup> Viral sequencing and variant identification were performed at the Virology laboratory of the Department of Medical Biotechnologies, University of Siena, Italy.

Neutralization assays of sera pre and one-hour post-infusion against their own isolates were performed at the Virology laboratory of the Infectious Disease Clinic, University of Perugia, as previously reported.<sup>12</sup>

Lastly, in patients with the viral isolate, we evaluated the NAbTs related to the viral variant and type of association.

The study was approved by Umbria regional Ethic Committee: MONO-COVID observational study, protocol number 21647/21/OV, 30/04/2021.

**Statistical Analysis.** Standard descriptive statistics were used to summarize data, such as mean, standard deviation (SD), and percentage. The data were expressed as mean  $\pm$  SD, frequencies, or percentages with 95% confidence intervals (95% CI). The Pearson Chi-square test was used to compare the distribution of categorical variables. Numeric variables normally distributed were analyzed by t-test, while variables that were not normally distributed were analyzed by Mann–Whitney test. A p-value  $< 0.05$  was considered for statistical significance. Patients' demographic, epidemiological, and clinical characteristics were compared between the two groups according to the combination of bamlanivimab /etesivimab or casirivimab/ imdevimab vs. bamlanivimab monotherapy.

SPSS statistical package release 24.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses.

**Results.** Seventy-nine outpatients received treatment with monoclonal combinations, 25 with bamlanivimab /etesivimab and 54 with casirivimab/imdevimab. Forty (50.6%) were male, and the average age was 64. Sixty patients were treated at the DH of Infectious Diseases

Clinic of Perugia, 19 at the Covid Hospital of Spoleto.

*Neutralizing activity pre and post monoclonal infusion in Perugia subgroup patients.* Only in 42 out of the 60 patients treated with a monoclonal combination in Perugia was the virus isolated: 17 were affected by a SARS-Cov-2 alpha, 23 by a delta, and two by a gamma variant infection. Twenty-two had already been vaccinated (2 with one dose), and 20 had not. Nevertheless, the evaluation of NAbTs towards its own viral isolate was performed in all of them before and one hour post infusion.

**Table 1a** shows the baseline NAbTs, related to the vaccination status and their own viral isolate.

All alpha and gamma variant infections occurred by May 2021, all delta between July and November. Among the 22 already vaccinated subjects, the delta variant was by far the most prevalent one (86.36%), whereas, among unvaccinated individuals, the alpha variant was the prevalent one (75%).

The infection occurred within four months in 14/22 vaccinated patients (11 delta, 2 alpha, and 1 gamma). At baseline, the NAbTs were  $\leq 1:10$  towards 17/22 of own viral isolates (1 alpha, 1 gamma, 15 delta), and 9 within 2 months of the vaccination. Instead, in the two delta patients with NAbTs of 1: 160, the infection occurred approximately 5 months after vaccination.

**Table 1a.** Baseline neutralizing activity for already vaccinated patients and not for SARS-CoV2.

NAbT		0	1:10	1:20	1:40	1:160
<b>Vaccinated</b>	<b>22</b>					
Alpha	2	1	/	/	1	/
Delta	19	7	8	/	2	2
Gamma	1	0	/	/	/	/
<b>Not Vaccinated</b>	<b>20</b>					
Alpha	15	15	/	/	/	/
Delta	4	2	1	1	/	/
Gamma	1	1	/	/	/	/
<b>Total</b>	<b>42</b>					

NAbT: titers of neutralizing antibodies.

**Table 1b.** Post infusion Neutralizing activity for the two different monoclonal combinations.

NAbT		0	1:20	1:320	1:640	1:1280	1:2560	1:5120	1:10240
<b>Casirivimab/imdevimab</b>	<b>29</b>								
Alpha	9						2	2	5
Delta	20						1	2	17
Gamma	0						/	/	/
<b>Bamlanivima/etesivimab</b>	<b>13</b>								
Alpha	8	/		1	2	4	1	/	/
Delta	3	/	1	1	/	/	1	/	/
Gamma	2	2							
<b>Total</b>	<b>42</b>								

NAbT: titers of neutralizing antibodies.

**Table 2.** Demographic, clinic and laboratory characteristics of patients treated with bamlanivimab (B) alone and with bamlanivimab etesevimab (L), casirivimab-imdevimab (R) associations.

	B	L/R	<i>p</i>
No. (%)	39	79 L 25 (31.6) R 54 (68.4)	
Monoclonal associations N (%)			
Age, mean (SD) [range], years	63.2 (15.8)	64 (15.0)	0.820
Male, No. (%)	20 (51.3)	40 (50.6)	0.0947
Caucasian, N (%)	39 (100.0)	68 (86.1)	0.14
Body mass index (BMI), Kg/m <sup>2</sup> mean (SD) [range]	29.2 (6.8)	29.5 (6.0)	0.804
<b>Comorbidities, No. (%)</b>			
BMI ≥35 kg/m <sup>2</sup>	15 (38.5)	31 (39.2)	0.935
Chronically undergoing peritoneal dialysis or hemodialysis	10 (25.6)	0	<0.001
Uncontrolled diabetes mellitus (HbA1c ≥9%) or with chronic complications	13 (33.3)	15 (19)	0.085
Secondary immunodeficiency (onco-haematological patient, immunosuppressive treatment)	11 (28.2)	14 (17.7)	0.190
Cardio-cerebrovascular disease (arterial hypertension with organ damage)	20 (51.3)	37 (46.8)	0.649
COPD and/or other chronic respiratory disease (pulmonary fibrosis or needing O <sub>2</sub> -therapy)	15 (38.5)	10 (12.7)	0.001
Primary immunodeficiency	10 (25.6)	2 (2.5)	<0.001
Congenital or acquired heart disease	10 (25.6)	3 (3.8)	<0.001
Neurodevelopmental disease	10 (25.6)	(0)	<0.001
<b>Vital Signs, mean (SD)</b>			
Temperature, °C, mean (SD)	36.7 (0.77)	36.8 (0.81)	0.706
Heart rate/min, mean (SD)	81.3 (12.5)	83.15 (12.7)	0.478
Respiratory rate/min, mean (SD)	18 (2.9)	17 (3.6)	0.097
Systolic blood pressure, mm/Hg, mean (SD)	125 (15.6)	130 (17.1)	0.107
Diastolic blood pressure, mm/Hg, mean (SD)	75.3 (9.9)	75.7 (12.1)	0.285
Oxygen saturation, % mean (SD)	96.5 (1.9)	96.08 (1.7)	0.151
<b>Vaccination</b>			
No. (%)	4 (10.3)	41 (51.9)	<0.001
2 doses	2 (5.1)	34 (43.0)	<0.001
<b>Genes detected No. (%)</b>			
N	38 (35.2)	70 (64.8)	0.838
S	1 (3)	32 (97)	0.997
E	29 (74.4)	47 (59.4)	0.197
Days from symptom' s onset to treatment, mean (SD)	4.23 (1.7)	4.24 (1.9)	0.978
Mild complications N (%)	12 (30.8)	8 (10.1)	0.005
Hospitalizations for all causes N (%)	8 (20.5%)	5 (6.3%)	0.021
Hospitalizations for Covid pneumonia N (%)	4 (10.3%)	5 (6.3%)	0.450

**Table 1b** shows the post-infusion NAbTs according to the type of mAbs. After casirivimab / imdevimab infusion, no patients affected by alpha or delta variants had NAbTs ≤ 1: 2560, 22 of them (75.86%) had NAbTs ≥ 10240. Instead, after bamlanivimab / etesevimab, in the two patients affected by gamma variant, no NAbTs were obtained; in 9/11 patients with alpha and delta variants (81.8%), NAbTs <1: 2560 and in 2 a titer of 1:2560 was seen. Noteworthy, different NAbTs in favor of casirivimab /imdevimab both for the alpha and delta variants were observed, and the statistical difference for

the alpha variant was very significant ( $p=0.001$ ). Two out of the 42 patients with viral isolation were hospitalized, both fully vaccinated, affected by delta variant, one treated with casirivimab / imdevimab, and one with bamlanivimab / etesevimab; Although they had been vaccinated two and three months earlier, both didn't have NAbTs at baseline. The patient on casirivimab/imdevimab had a post-infusion NAbTs of 1: 10240, the treated one with bamlanivimab / etesevimab of 1: 320.

Overall clinical efficacy of two monoclonal antibodies associations in Umbria. **Table 2** shows the demographic, clinical, and virological characteristics of all the patients treated with the mAbs combinations from April to November 2021 related to those of patients previously treated with bamlanivimab monotherapy. The most frequent comorbidities observed did not statistically differ from the observed ones in the previous study. However, renal insufficiency in dialysis, chronic obstructive pulmonary disease, and congenital or acquired cardiovascular diseases were less represented.

The diagnosis was performed with a molecular assessment. Genes N, S, and E were detected by PCR assay in 70/79, 32/79, and 47/79, respectively. In addition, the S deletion, suggestive of the alpha variant, was observed in 47 patients (59.5%), unlike in the previous experience (almost all the cases).

The vaccination rate was different ( $p < 0.001$ ). Fifty-two percent of the subjects had been vaccinated with at least one dose, 43% with two doses compared to 10% and 5%, respectively. Most of the unvaccinated were observed in May and June.

Baseline vital signs were comparable to the previous experience, and some main symptoms such as fever and asthenia but not myalgia and dyspnea.

The mAbs infusion occurred about four days after the onset of symptoms, and no adverse reactions were observed. Bamlanivimab/etesivimab was infused on 12 S drop out viral isolates (48%) and casirivimab /etesivimab on 35 (64.8%).

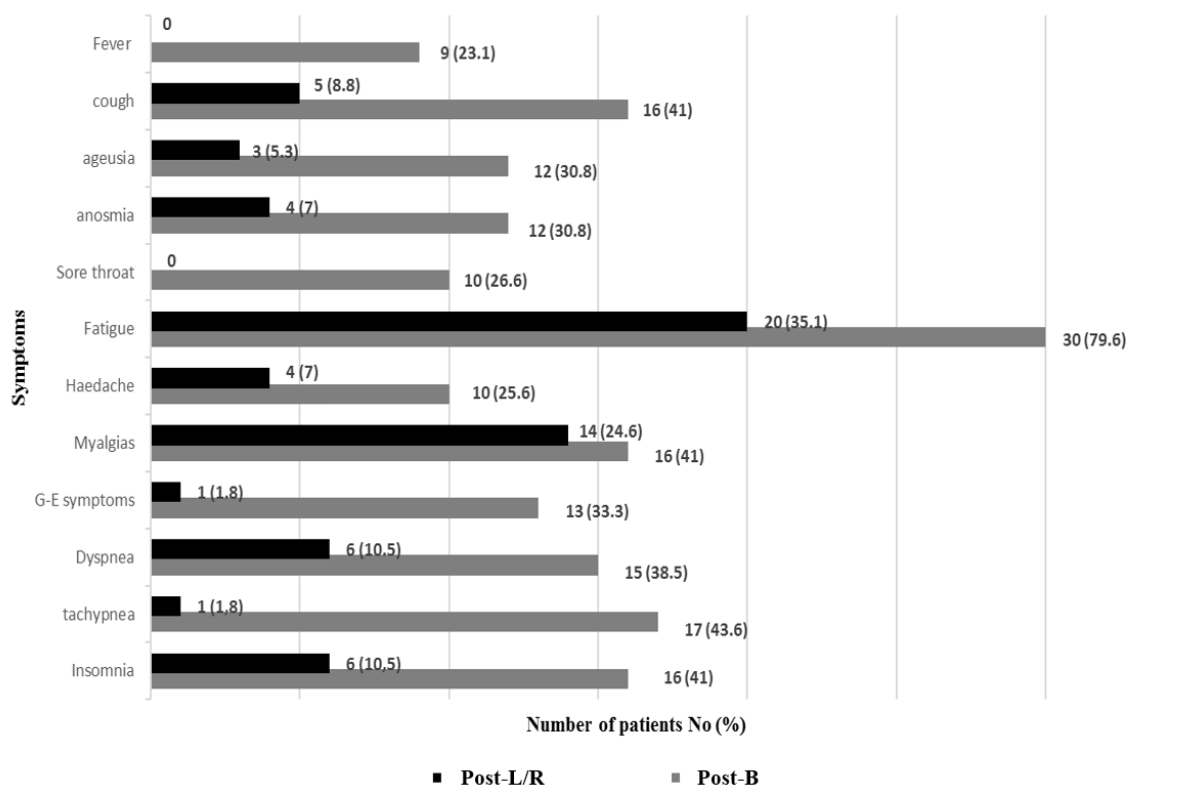
In the following 30 days, 5/79 (6.3%) patients were hospitalized for COVID 19 pneumonia.

One of the 5 hospitalized patients was unvaccinated (1/38, 2.63%). Overall, 2 patients showed a gene S drop out at the PCR assay and were considered alpha variants, 2 were delta variants (viral isolation and sequencing), 1 expressed S gene and was of uncertain attribution. The 2 delta infections appeared 2 and 3 months after vaccination, while the 2 alpha infections 6 and 7 months after. The untyped variant hospitalization was related to the unvaccinated patient. The 2 S gene dropout variants had been treated with casirivimab /etesivimab as well as one delta variant and the isolate of uncertain attribution, while one delta variant with bamlanivimab/etesivimab.

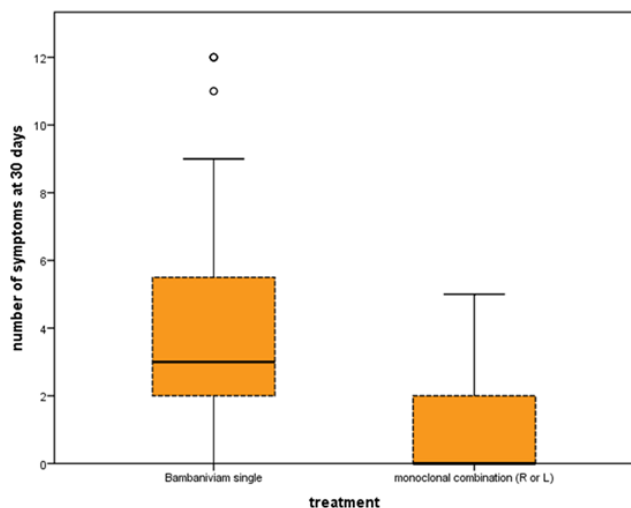
The secondary outcome about the global hospitalization rate was observed, 6.3 % vs 20.5% in the previous experience ( $p = 0.021$ ), but the COVID19 pneumonia hospitalization (6.5% vs 10%,  $p = 0.45$ ), and the alpha variant pneumonia (4.25 % vs 10.25%,  $p = 0.274$ ) weren't reached. Cardiovascular disease (60%), BMI  $\geq 35$  (40%), uncontrolled diabetes mellitus (20%), secondary immunodeficiency (20%), COPD (20%) were the main comorbidities.

Thirty days after the infusion, the most common symptoms were less represented (**Graphic 1**).

It should be noted that insomnia, not present at baseline in both groups of patients, was present thirty days after the infusion. Therefore, the symptom numbers as shown in **Figure 1** are significantly lower at 30 days in Abs combination vs. monotherapy.



**Graphic 1.** Symptoms 30 days after treatment of bamlanivimab –etesivimab or casirivimab-imdevimab (L/R) and bamlanivimab. (B) alone.



**Figure 1.** Number of symptoms at 30 days after monoclonal therapy between patients treated with Bamlanivimab alone versus the two combinations bamlanivimab /etesevimab (L) or casirivimab/imdevimab (R) (Mann–Whitney U test).

**Discussion and Conclusions.** This study is an extension of our previous experience in treating COVID 19 with bamlanivimab monotherapy until its revocation.<sup>10</sup> It refers to the subsequent use of the monoclonal combinations casirivimab/imdevimab and bamlanivimab/ etesevimab from late April to November 2021 in Umbria. Still, particular aspects of this study consist in having evaluated in a subgroup of patients, before and after the infusion, the neutralizing activity of their serum towards its own viral isolate.

The spread of the SARS COV 2 virus in this period was characterized by an initial prevalence of the alpha variant (B.1.1.7) and its progressive substitution with the delta variant (B.1.617.2). Moreover, recent data have shown the delta variant to be resistant to neutralization by anti-RBD mAbs, including bamlanivimab.<sup>13</sup> In Italy, the delta variant emerged in May 2021; from July 20 its prevalence was 94.8%, while the alpha variant was 3.2%.<sup>14</sup> However, we suspended this observational study in November 2021 due to the rapid and progressive spread of the omicron variant (B.1.1.529) because, very early, it proved to be resistant to the two mAbs combinations in use until then.<sup>15</sup>

Our study is observational, not randomized, and conditioned by mAbs combinations available at the hospital pharmacies on that given day.

Elements of interest consist in having isolated in 42 patients from Perugia the viral variant and evaluated the NAbTs before and after the infusion towards its own viral isolate, in the context of an overall population different from the previous experience<sup>10</sup> by risk factors, vaccination status, involved VOCs and type of mAbs treatment.

The comorbidities reported in this whole experience highlight a set of patients with a lower risk of progression compared to those treated with bamlanivimab alone. Overall, the global threat of hospitalization was lower

than previously observed; however, half of the cases were determined by a worsening of their comorbidities.

Our data show a higher hospitalization risk than that observed in the randomized trials,<sup>5,6</sup> but in line with other experiences drawn from real-life.<sup>9</sup>

Both combinations of mAbs, made from NAb convalescent COVID-19 patients infected in the first half of 2020 and evaluated before the news VOCs, cannot equally counteract the viral variants that subsequently spread. Moreover, in this study, which also involves patients with the delta variant that has been circulating in Italy since May 2020, the hospitalization rate for the alpha variant was 4.25% (2/47), in line with the report by Falcone et al. for the same variant.<sup>9</sup> However, the risk was higher in the remaining cases, equal to 9.37% and 8.7% for delta, as a disharmonious use of combinations. In fact, in the 20 treated patients with casirivimab/imdevimab, the risk of hospitalization was only 5%, and in the 3 treated with bamlanivimab/etesevimab was 33%.

Eighty percent of hospitalized patients were vaccinated (4/5) with two doses. However, the time-lapse from the vaccination was greater than 6 months for the alpha variant and 2 and 3 months for delta. The hospitalization rate was 9.75% and 2.63% for unvaccinated individuals.

Thirty days after the infusion of the mAbs, an important improvement in symptoms was observed, independent of treatment timing, viral variant, vaccination status, and type of monoclonal combinations (**Graphic 1** and **Figure 1**). In addition, the rate of sequelae at 30 days appears in line with the observations made close to the infection.<sup>16,17</sup>

The sub-study performed in Perugia made it possible to investigate some pathogenic aspects of the infection and the sensitivity of viral isolates to mAbs infused. Indeed, the viral agent's isolation, characterization, and sequencing were possible in 42/60 patients, 22 vaccinated (two with one dose and both with alpha infection), and 20 unvaccinated. Among the 22 vaccinated subjects, the delta variant was by far the most prevalent one (19/22), whereas, among unvaccinated individuals, the alpha variant was the prevalent one (15/20). Moreover, it should be emphasized that 11 delta variant infected patients had been vaccinated within 4 months, most of the nineteen didn't have neutralizing activity at baseline, and, worth highlighting, half of these last had been vaccinated in the previous two months.

These data are in line with those in the literature. In a study in which the neutralizing activity of the serum of subjects vaccinated with BNT162b2 was studied against SARS-CoV-2 VOCs, a lower protective efficacy against the delta and alpha variants compared to the wild type and for the delta versus alpha was documented, as well as a significant reduction in the NAbTs over time for all VOCs and not protective NAbTs at 3 months for some

subjects towards beta and delta isolates.<sup>18</sup> To be emphasized is that the absence of the neutralizing activity observed in most of our patients with delta infection at 2-3 months can be explained by the different characteristics of our patients (infected versus healthy subjects).

The inevitable consequence is that, in the physiological decline of the antibody response after vaccination, the protective efficacy decays earlier for the variants towards which the baseline neutralizing activity is lower.

Our data can be supported by a greater diffusion capacity of the delta variant and the simultaneous progression of the vaccination campaign without a cause/effect relation, but also by a greater sensitivity of the alpha variant to the vaccination so that more easily delta variant took over.

Our data about the neutralizing activity after infusion are also worthy of interest. The greater neutralizing efficacy of casirivimab /imdevimab may be justified by the action of the two monoclonals on different antigenic epitopes of protein S, unlike antigenic overlapping with bamlanivimab/etesivimab. Moreover, the poor efficacy against the delta variant of bamlanivimab/etesivimab can be explained by the presence of L452R, an escape mutation for bamlanivimab.<sup>19</sup>

Indeed, monoclonal antibodies targeting immunodominant epitopes of the spike are susceptible to a different efficacy in variants characterized by other mutations in protein S.

Therefore, there is a need for different therapeutic options available simultaneously with potential activity against different viral variants, given the need to provide treatment with mAbs in a very short time.

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**Conclusions.** some indications can be drawn from our report, which was done in the presence of two dominant VOCs (alpha and delta).

Although a poor sample, this clinical study demonstrated better efficacy of the mAbs combinations relative to monotherapy, although fewer risk factors were present.

In this experience, we have been unable to choose the type of mAbs, at least based on gene S dropout, due to the conditioned availability at the hospital pharmacies on that given day.

Alpha variant infections occurred mainly in unvaccinated subjects, after the first dose or after 5-6 months from the vaccination; delta infections usually occurred within four months of full vaccination.

NAb activity at baseline against its own isolate was practically absent in most subjects.

A different NAb activity of the two associations was seen (casirivimab /imdevimab > bamlanivimab /etesevimab).

The difficulty in proposing targeted mAbs, in a context of a rapid succession of new viral variants and a missing context of adequate and rapid viral sequencing leads to an even wider utilization of drugs that inhibit viral replication.

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