

REGEN-COV antibody cocktail (casirivimab/imdevimab) for the treatment of inpatients with early hospital-acquired COVID-19: a single center experience

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Abstract

Inpatients with hospital-acquired (HA) COVID-19 have mortality rates above 30%. Subjects with early diagnosis of COVID-19 and risk factors for disease progression are suitable for treatment with anti-SARS-CoV-2 neutralizing monoclonal antibodies (mAbs). We retrospectively assessed the outcome of a cohort of hospitalized patients with laboratory confirmed SARS-CoV-2 nosocomial infection who were admitted to the COVID-19 general ward of an acute-care Italian hospital between October 25, 2020 and April 30, 2021. Patients receiving the REGEN-COV mAb cocktail (casirivimab/imdevimab) were compared with those receiving standard care.

Of 34 patients, 11 (mean age, 73.1; 9 males) underwent treatment with REGEN-COV and 23 received standard care. The 2 study groups were well balanced regarding age, sex, comorbidities, acute illness severity at diagnosis of SARS-CoV-2 infection, and all participants had at least 2 risk factors for disease progression. Five of 11 patients in the REGEN-COV group and 16 of 23 in the standard care group were asymptomatic at diagnosis; the remaining had symptoms of mild COVID-19. All patients received REGEN-COV within 3 days of infection confirmation. Treatment with REGEN-COV was inversely associated with oxygen requirement for COVID-19 during hospital stay (OR 0.02, CI 0–0.52, $p=0.0174$). No 28-day deaths were registered in the REGEN-COV group, compared to 8 (34.8%) in the standard care group ($p=0.0339$). Kaplan-Meier analysis confirmed the survival advantage of REGEN-COV group (log-rank $p=0.00324$). No serious adverse events related to REGEN-COV administration were recorded.

Based on these findings, REGEN-COV appears safe and might prevent disease progression in high-risk inpatients with early diagnosis of HA-COVID-19.

Introduction

During the first surge of the COVID-19 pandemic, up to 15% of COVID-19 inpatient cases have been reported as hospital-acquired (HA) [1–6]. Patients admitted to hospital are often elderly and affected by multiple comorbidities, making them vulnerable to complications resulting from SARS-CoV-2 infections [1, 3, 5, 7]. Previous studies have shown high mortality rates in patients acquiring COVID-19 during hospital admission for other medical reasons, ranging between 21.6 and 36% [1, 4, 7, 8].

The implementation of rigorous infection prevention and control measures, and the increasing vaccination coverage of healthcare workers and hospitalized individuals have permitted to reduce considerably the spread of SARS-CoV-2 in the hospital setting. However, the risk of acquiring COVID-19 during hospital stay remains non-negligible, since preventive strategies are not infallible and introduction of SARS-CoV-2 into the facility can occur especially from patients, hospital staff, or visitors with pre- or asymptomatic infection [1, 9–12].

To avoid progression toward severe COVID-19 and its sequelae, inpatients who acquire nosocomial SARS-CoV-2 infection need prompt diagnostic and effective therapeutic management. To date, limited treatment options are available for COVID-19. Remdesivir is the only antiviral agent approved, which has

been shown to reduce time to recovery in patients hospitalized with severe COVID-19 [13]. Dexamethasone decrease mortality in inpatients with severe to critical disease requiring oxygen support or mechanical ventilation [14]. However, no treatments have been approved that can be administered early in the course of infection to prevent severe illness and its complications [15].

Recently, attention has been focused on neutralizing anti-SARS-CoV-2 monoclonal antibodies (mAbs), a novel class of antiviral drugs under investigation, which might limit disease progression in patients in the early phases of COVID-19, by providing immediate, passive immunity [16, 17]. REGEN-COV is a cocktail of two fully human non-competing mAbs –casirivimab and imdevimab– that bind to 2 different sites on the receptor binding domain of the SARS-CoV-2 spike protein, thereby preventing viral entry into the host cell [18]. Based on limited available evidence, REGEN-COV has been granted an emergency use authorization (EUA) from US FDA for the treatment of high-risk outpatients with mild to moderate COVID-19 [19]. Accordingly, the European Medicines Agency (EMA) and the Italian Medicines Agency (AIFA) have issued a favorable advice on the use of the casirivimab/imdevimab cocktail in subjects with confirmed SARS-CoV-2 infection not requiring supplemental oxygen for COVID-19 and who are at high risk of progressing to severe disease [20, 21].

The chance of making a timely diagnosis of SARS-CoV-2 infection by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing in patients admitted to hospital for other medical illnesses, and the absence of logistic obstacles to the use of intravenous drugs in the hospital setting, make individuals with HA-COVID-19 particularly suitable for treatment with mAbs. The purpose of the present study is to describe the characteristics and outcomes of a cohort of inpatients who were diagnosed with HA-COVID-19 and underwent early treatment with the REGEN-COV mAb cocktail.

Methods

Study design and participants

This retrospective observational study was performed at the San Giovanni di Dio hospital of Florence, Italy, an acute-care hospital with 296 beds. We consecutively enrolled all patients who were diagnosed with HA-COVID-19 during hospitalization for other medical reasons and were transferred to the dedicated COVID-19 general ward between October 25, 2020 and April 30, 2021. Diagnosis of SARS-CoV-2 infection was confirmed by RT-PCR assay on nasopharyngeal swab. All participants received treatment in accordance with current guidelines. Individuals with mild or moderate HA-COVID-19 were treated with supportive therapy, while patients experiencing progression to severe disease additionally received remdesivir, dexamethasone, and respiratory support as appropriate [22]. Critically ill patients requiring mechanical ventilation were transferred to the intensive care unit (ICU), unless a “do not intubate” order was present. Starting from March 2021, neutralizing mAbs were made available at our institution. Since that time, a non-random subset of patients with nosocomial SARS-CoV-2 infection were offered early treatment with REGEN-COV, in addition to standard care. To assess the effect of the

casirivimab/imdevimab combination therapy, these subjects (REGEN-COV group) were compared with those receiving the conventional treatment only (standard care group).

Hospital protocol for SARS-CoV-2 infection prevention and control

During the study period, a comprehensive infection prevention and control program was in place at our institution to promptly identify SARS-CoV-2 infected individuals and contrast COVID-19 nosocomial transmission, including: dedicated COVID-19 wards for management of SARS-CoV-2 infected patients, universal masking, supply of proper protective personal equipment for all healthcare workers, banning of visitors, symptom-directed and universal testing for SARS-CoV-2 infection by RT-PCR on nasopharyngeal swab. According to the hospital protocol, all patients underwent RT-PCR testing on admission, regardless of symptoms. Subsequently, all patients admitted to non-COVID-19 wards underwent serial screening for SARS-CoV-2 infection, repeating nasopharyngeal swab on the second day and thereafter every 5 days. Patients with laboratory confirmed COVID-19 were promptly transferred to the dedicated ward. In the absence of overt symptoms, 2 positive RT-PCR test results (obtained less than 12 hours apart) were required to confirm SARS-CoV-2 infection and dispose transfer to the COVID-19 ward. Close contacts of COVID-19 cases were quarantined and daily tested by nasopharyngeal swab.

Diagnosis of HA-COVID-19

Diagnosis of HA-COVID-19 was made in accordance with the official European Centre for Disease Prevention and Control (ECDC) definition of HA-COVID-19 cases [23]. In particular, a diagnosis of *probable* HA-COVID-19 was made in inpatients with no clinical suspicion of disease and negative RT-PCR test on hospital admission, and with 1) symptom onset and/or SARS-CoV-2 identification by RT-PCR on day 8-14 after admission, or 2) symptom onset and/or SARS-CoV-2 identification by RT-PCR on day 3-7 and a strong suspicion of healthcare transmission (e.g., in-hospital contact with a COVID-19 index case). A diagnosis of *definite* HA-COVID-19 was made in inpatients with symptom onset and/or SARS-CoV-2 identification by RT-PCR on day >14 after admission.

Treatment with REGEN-COV

REGEN-COV treatment was administered at the discretion of the attending physician. In accordance with the recommendations of the AIFA [21], patients with HA-COVID-19 were considered eligible for treatment with the casirivimab/imdevimab cocktail if they 1) did not require supplemental oxygen for COVID-19 pneumonia, 2) had at least 1 risk factor for progression to severe COVID-19, 3) had symptoms consistent with mild or moderate COVID-19 for less than 10 days and a confirmation of SARS-CoV-2 infection by RT-PCR. Besides these criteria, asymptomatic HA-COVID-19 patients were also considered eligible if they had a high risk of severe disease and a laboratory diagnosis of SARS-CoV-2 infection obtained by RT-PCR test less than 3 days prior of mAbs infusion.

Risk factors for disease progression included: age ≥ 65 years (associated with at least 1 other risk factor), obesity (BMI ≥ 35), cerebrovascular and cardiovascular disease, hypertension, chronic lung disease,

including asthma, type 1 or 2 diabetes mellitus, chronic kidney disease or dialysis, chronic liver disease, immunosuppression, HIV infection, sickle cell anemia, thalassemia.

Patients selected for treatment were requested to sign an informed consent form for emergency use of REGEN-COV, as required by the Hospital Management. In case of acceptance, they received a single intravenous administration of 1200 mg of casirivimab and 1200 mg of imdevimab, diluted together in 250 mL of normal saline and infused over 60 minutes.

Outcomes

The main outcomes of the study were the need for supplemental oxygen due to COVID-19, all-cause mortality by 28 days after diagnosis of SARS-CoV-2 infection and adverse events related to REGEN-COV administration.

Data collection

For each patient enrolled to the study, demographic, clinical, laboratory, treatment and outcome data were retrieved from hospital electronic medical records. When needed, data of interest to the study registered after discharge of patients toward other health facilities were collected by consulting the electronic charts of the host structures.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation (SD) and compared by T-test, Satterthwaite T-test or Mann-Whitney, according to Shapiro-Wilk test for normality and F-test for variance equality. Categorical variables were expressed as numbers and percentages and compared by Chi-square test or Fisher exact test, as appropriate. A simple logistic regression model was used to evaluate the association between supplemental oxygen requirement and treatment groups. Odds ratio (OR) and its 95% confidence interval (CI) were reported. 28-day survival curves were estimated using the Kaplan-Meier method and the differences in survival between the study groups were assessed by a log-rank test. All data were analyzed using SAS 9.3 (SAS Institute, Cary, North Carolina).

Results

During the study period 34 patients (mean age, 77 ± 12.9 , 12 females) were diagnosed with HA-COVID-19 and transferred to the COVID-19 ward; in particular, 26 subjects were categorized as *probable* and the remaining as *definite* HA-COVID-19 cases. None of them had been vaccinated for SARS-CoV-2 at the time of diagnosis. Twenty-three of the 34 enrolled patients (mean age, 78.9 ± 14.6 ; 10 females) received conventional therapies for COVID-19 (standard care group), while 11 patients (mean age, 73.1 ± 7.4 ; 2 females) were treated with REGEN-COV in addition to standard care (REGEN-COV group). Baseline characteristics of participants are shown in Table 1. The 2 treatment groups were well balanced regarding age, sex, comorbidities (Charlson comorbidity index) and acute illness severity at confirmation of SARS-CoV-2 infection, as assessed by the National Early Warning Score 2 (NEWS2). All patients had at least 2 risk factors for progression to severe disease. Five of 11 (45.5%) patients in the REGEN-COV group and 16

of 23 (69.6%) in the standard care group were asymptomatic at the time of SARS-CoV-2 infection confirmation by RT-PCR test, the remaining being symptomatic for mild COVID-19. The only clinical manifestation reported in all symptomatic subjects was mild to moderate fever. None of participants were on oxygen support for COVID-19 at diagnosis.

Table 1
Baseline characteristics of enrolled patients

Variables	All patients (n=34)	Patients treated with REGEN-COV (n=11)	Patients treated with standard care (n=23)	P value
Mean age, years (\pm SD)	77 (\pm 12.9)	73.1 (\pm 7.4)	78.9 (\pm 14.6)	0.1350
Female sex, n (%)	12 (35.3)	2 (18.2)	10 (43.5)	0.2525
Primary admission department, n (%)				
Internal medicine	23 (67.6)	9 (81.8)	14 (60.9)	0.2714
General surgery	1 (2.9)	0 (0)	1 (4.3)	1.0000
Neurosurgery	1 (2.9)	1 (9.1)	0 (0)	0.3235
Orthopedics	9 (26.5)	1 (9.1)	8 (34.8)	0.2137
Number of days from hospital admission to COVID-19 diagnosis, mean (\pm SD)	12 (\pm 10.8)	14.1 (\pm 11.2)	11 (\pm 10.7)	0.4430
NEWS2 at diagnosis of COVID-19, mean (\pm SD)	1.9 (\pm 1.5)	2 (\pm 1)	1.9 (\pm 1.6)	0.8800
Presence of symptoms at diagnosis of COVID-19, n (%)	13 (38.2)	6 (54.5)	7 (30.4)	0.2619
SARS-CoV-2 antibody test result at diagnosis of COVID-19, n (%)				
Positive	2 (5.9)	0 (0)	2 (8.7)	0.549
Negative	20 (58.8)	7 (63.6)	13 (56.5)	0.7288
Missing	12 (35.3)	4 (36.4)	8 (34.8)	1.0000
Risk factors				
Age \geq 65 years, n (%)	30 (88.2)	1 (90.9)	3 (87)	1.0000
Hypertension, n (%)	24 (70.6)	8 (72.7)	16 (69.6)	1.0000
Diabetes, n (%)	13 (38.2)	5 (45.5)	8 (34.8)	0.5491

Variables	All patients (n=34)	Patients treated with REGEN-COV (n=11)	Patients treated with standard care (n=23)	P value
Cardiovascular disease, n (%)	21 (61.8)	5 (45.5)	16 (69.6)	0.1759
Cerebrovascular disease, n (%)	11 (32.4)	4 (36.4)	7 (30.4)	1.0000
COPD, n (%)	8 (23.5)	4 (36.4)	4 (17.4)	0.3884
Obesity (BMI \geq 35), n (%)	1 (2.9)	1 (9.1)	0 (0)	0.3235
Malignancy, n (%)	6 (17.7)	1 (9.1)	5 (21.7)	0.6379
Chronic renal failure, n (%)	6 (17.7)	2 (18.2)	4 (17.4)	1.0000
Chronic liver disease, n (%)	2 (5.9)	1 (9.1)	1 (4.4)	1.0000
Immunodeficiency, n (%)	1 (2.9)	1 (9.1)	0 (0)	0.3235
Charlson Comorbidity Index, mean (SD)	6.5 (\pm 3.3)	6.2 (\pm 3)	6.7 (\pm 3.5)	0.7057
Number of comorbidities, mean (SD)	3.2 (\pm 1.4)	3.4 (\pm 1.3)	3.2 (\pm 1.5)	0.7074

All patients in the REGEN-COV group received the mAb cocktail infusion within 3 days of SARS-CoV-2 infection confirmation (on average, 42.7 ± 11.3 hours after infection confirmation). All symptomatic patients received REGEN-COV within 4 days of symptom onset (on average, 55.5 ± 15.1 hours after symptom onset).

Table 2 illustrates laboratory findings, treatments and outcomes of the study population. Among the main biochemical markers measured 5-10 days after COVID-19 diagnosis, only C reactive protein (CRP) was significantly higher in the standard care group than in the REGEN-COV group (8.2 vs 2.5, $p=0.0136$). None of patients who received treatment with REGEN-COV required supplemental oxygen for COVID-19 pneumonia during hospital stay, compared to 15 (65.2%) among patients treated with standard care ($p=0.0005$). Moreover, none of patients receiving the REGEN-COV required dexamethasone treatment, versus 16 (69.6%) patients in the standard care group ($p=0.0099$). A diagnosis of interstitial pneumonia was made by chest ultrasound (US), chest X-ray, or computed tomography (CT) in 2 (18.2%) and 18 (78.3%) patients in the REGEN-COV group and the standard care group, respectively ($p=0.0020$). No deaths were registered within 28 days after COVID-19 diagnosis in the REGEN-COV group, compared to 8 (34.8%) in the standard care group ($p=0.0339$). No participant in either group underwent endotracheal intubation or ICU transfer due to COVID-19 complications. Two patients in the REGEN-COV group were transferred to ICU due to events unrelated to COVID-19 or mAb cocktail infusion.

Table 2
Laboratory findings, treatments and outcomes of enrolled patients

Variables	All patients (n=34)	Patients treated with REGEN-COV (n=11)	Patients treated with standard care (n=23)	P value
Main laboratory findings*				
White blood cell, x10 ⁹ /L, mean (±SD)	9.3 (±4.6)	8.1 (±3.4)	9.8 (±5.1)	0.3247
Lymphocyte, x10 ⁹ /L, mean (±SD)	1.5 (±1.2)	1.7 (±0.7)	1.6 (±1.4)	0.8252
C reactive protein, mg/L, mean (±SD)	6.4 (±6.4)	2.5 (±1.6)	8.2 (±7.1)	0.0136
ALT/SGPT, U/L, mean (±SD)	29.7 (±21.4)	32.4 (±17)	28.4 (±23.4)	0.6170
D-dimer, ng/mL, mean (±SD)	3216 (±2978)	4477 (±4063)	2613 (±2151)	0.0878
COVID-19 related treatments				
LMWH, n (%)	26 (76.5)	6 (54.5)	20 (87)	0.0789
Desamethasone, n (%)	16 (47.1)	0 (0)	16 (69.6)	0.0099
Remdesivir, n (%)	8 (23.5)	0 (0)	8 (34.8)	0.0339
Outcome measures				
Need of supplemental oxygen for COVID-19, n (%)	15 (44.1%)	0 (0%)	15 (65.2%)	0.0005
28-day all cause death, n (%)	8 (23.5%)	0 (0%)	8 (34.8%)	0.0339
Fever, n (%)	17 (50%)	5 (45.5%)	12 (52.2%)	0.7139
COVID-19 typical imaging findings (X-ray, US, CT), n (%)	20 (58.8%)	2 (18.2%)	18 (78.3%)	0.0020
Need of NIPPV for COVID-19, n (%)	5 (14.7%)	0 (0%)	5 (21.7%)	0.1499
Length of hospital stay, post-infection, days, mean (±SD)	14 (±14.6)	16.5 (±15.6)	12.8 (±14.6)	0.5063

* Blood sample obtained 5-10 days after SARS-CoV-2 infection diagnosis

** Analysis limited to 23 patients: 11 of 34 enrolled patients died while still having a positive RT-PCR test, and were excluded

Variables	All patients (n=34)	Patients treated with REGEN-COV (n=11)	Patients treated with standard care (n=23)	P value
Time to negative swab, days, mean (\pm SD)**	39.4 (\pm 22.7)	26.1 (\pm 12.8)	49.7 (\pm 23.6)	0.0097
* Blood sample obtained 5-10 days after SARS-CoV-2 infection diagnosis				
** Analysis limited to 23 patients: 11 of 34 enrolled patients died while still having a positive RT-PCR test, and were excluded				

The regression logistic analysis confirmed that the casirivimab/imdevimab combination treatment was inversely associated with the supplemental oxygen requirement for COVID-19 (OR 0.02, CI 0–0.52, p 0.0174). The Kaplan-Meier analysis showed a significant survival advantage for REGEN-COV treated patients compared to those receiving standard care alone (log-rank p=0.00324) (figure 1).

Regarding the adverse events potentially related to the mAb cocktail treatment, 3 (27.3%) patients experienced low grade fever within 2 hours of REGEN-COV infusion. No other adverse events were registered.

All participants underwent periodic testing for SARS-CoV-2 by RT-PCR on nasopharyngeal swab: the first negative test was obtained on average 26.1 ± 12.8 and 49.7 ± 23.6 days after infection diagnosis in patients treated with REGEN-COV and in those receiving standard care, respectively (p=0.0097).

Discussion

The results of the present study showed a better outcome, in terms of supplemental oxygen requirement for COVID-19 and all-cause mortality, in high-risk inpatients with hospital-acquired SARS-CoV-2 infection receiving early treatment with REGEN-COV, compared to those receiving standard care alone. None of patients treated with the casirivimab/imdevimab cocktail experienced disease progression or death within 28 days, despite all having multiple risk factors for development of severe COVID-19. Conversely, 60% of patients receiving standard care experienced acute hypoxemic respiratory failure requiring oxygen support, and almost 35% of them died within 28 days of SARS-CoV-2 infection diagnosis, a finding consistent with results of previous investigations on HA-COVID-19 [1, 4, 7, 8]. Administration of REGEN-COV was well tolerated and no serious adverse events were registered in treated patients during hospital stay.

Of note, patients in the REGEN-COV group received the mAb cocktail in the early phases of the SARS-CoV-2 infection, as supported by the low severity of the disease at diagnosis and the absence of an endogenous immune response against SARS-CoV-2 in all 7 patients who underwent serology assay (4 patients were not tested for serum antibodies against SARS-CoV-2). A prompt diagnosis of nosocomial SARS-CoV-2 infection was favored by the institutional protocol for COVID-19 prevention and control, which provided for symptom-oriented testing and serial universal screening of all hospitalized patients by

RT-PCR on nasopharyngeal swab. As shown by previous studies, a timely infusion of mAb therapy in the early phases of COVID-19 is needed in order to achieve beneficial effects, as mAbs appears ineffective if administered late in the disease course, when severe symptoms have developed [16, 24–26].

Our findings appear in line with the results of the large phase 1-3 randomized controlled trials by Weinreich and colleagues, which assessed REGEN-COV treatment in non-hospitalized COVID-19 patients [27, 28]. In the final analysis of this trial, including 4057 ambulatory patients with early diagnosis of symptomatic COVID-19 and at least 1 risk factors for severe disease, REGEN-COV, both in the 2400mg and 1200mg dosage, was safe and significantly reduced COVID-19-related hospitalization or all-cause death compared to placebo (71.3% reduction [1.3% vs 4.6%; $p < 0.001$] and 70.4% reduction [1.0% vs 3.2%; $p = 0.002$], respectively) [27].

To date, few data are available on the use of mAbs in the special population of patients acquiring COVID-19 during hospital admission for other medical illnesses. Koehler and colleagues have described the outcome of 11 asymptomatic patients with HA-COVID-19 admitted to a German hospital, who received a treatment with different mAbs (bamlanivimab in 8 patients, and casirivimab/imdevimab in 3 patients) early after infection diagnosis. Compared to 32 HA-COVID-19 asymptomatic patients receiving standard care alone, a lower rate of COVID-19-associated radiological changes and a remarkably lower rate of ICU admission and death were detected in subjects receiving mAbs [28]. The results of our study corroborate these findings and offer support to the use of REGEN-COV in high-risk inpatients who acquire asymptomatic to mild nosocomial COVID-19.

One notable ancillary finding of our study is the shorter time required to obtain a negative RT-PCR test on nasopharyngeal swab in patients treated with REGEN-COV compared to those treated with standard care. This result may appear not clinically relevant; however, it should be considered that faster viral clearance shortens the duration of isolation measures, thus accelerating the return of COVID-19 patients to community life. In addition, a reduced time to negative RT-PCR test could be especially important in COVID-19 patients admitted to hospital for underlying diseases requiring surgery or rehabilitation care, as a positive result of SARS-CoV-2 testing could preclude access to these services.

Although neutralizing mAbs have been validated as therapeutic option against COVID-19, circulating SARS-CoV-2 variants may show resistance to these antiviral agents, due to mutations that affect the targeted epitopes in the spike protein reducing or preventing antibody binding [17]. On April 2021, the FDA revoked the EUA for the bamlanivimab mAb monotherapy due to resistance in several major virus variants, including Delta variant and, more recently, it recommended against the use of the bamlanivimab/etesevimab cocktail in several US territories, due to high prevalence of variants with reduced susceptibility to both antibodies in the combination [29–32]. Although we have not ascertained the presence of infections by SARS-CoV-2 variants of concern (VOC) in our study, multiple analyses have shown that the combination of antibodies in REGEN-COV retains potency against major circulating VOCs, including Delta (B.1.617.2), which remains, to date, the dominant strain worldwide (source: GISAID) [30, 31]. Regarding the new Omicron (B.1.1.529) variant, recently identified in South Africa, there is no direct

evidence to support resistance or susceptibility to mAb therapies, including REGEN-COV. Prior in vitro analyses and structural modeling regarding the individual mutations present in the Omicron variant indicate a potential reduced neutralization activity of REGEN-COV antibodies; however, further analyses are needed to confirm and quantify this preliminary finding [33].

REGEN-COV and other neutralizing mAbs have been authorized based on studies conducted at a time in which SARS-CoV-2 vaccination was poorly widespread. As a consequence, we have little information on the benefits of mAbs in vaccinated patients who acquire SARS-CoV-2 infection. Casirivimab/imdevimab cocktail and the other authorized mAbs could be useful for the treatment of breakthrough COVID-19 in high-risk individuals with poor immune response to the vaccine or waning immunity, and in patients infected by SARS-CoV-2 variants for whom the immune response elicited by vaccination might be sub-optimal. Recently, Bierle and colleagues have assessed the efficacy of mAb treatment in a cohort of 1395 fully vaccinated persons with breakthrough COVID-19. In this cohort 107 (7.7%) patients required hospital admission by day 28; the risk of hospitalization was significantly lower in patients who were treated with mAb therapy, most of whom received casirivimab/imdevimab (OR 0.227, CI 0.128 - 0.403, $p < 0.001$) [34].

The strengths of this retrospective, real-world study are the assessment of a unique type of neutralizing mAb combination (casirivimab/imdevimab), and the exploration of its effect in a special cohort of inpatients affected by nosocomial COVID-19. Patients who acquire SARS-CoV-2 infection during hospital admission for reasons other than COVID-19 are often characterized by advanced age and a high burden of comorbidities; in addition, they have an underlying acute illness that could further increase vulnerability to complications and death from SARS-CoV-2 infection [12]. Our findings shed light on the possible therapeutic management of such high-risk patients.

This research has several limitations. The limited number of patients enrolled, the retrospective and monocentric design affect the validity, reliability and generalizability of the study results. Another limitation is that we were unable to accurately assess minor symptoms of SARS-CoV-2 infection (e.g., change in smell or taste, cough), which were not systematically reported in medical records. Finally, we were unable to identify the SARS-CoV-2 variants responsible for infection in the study population, as enrolled patients did not undergo viral genome sequencing, and we could not assess the presence of a correlation between viral variants responsible for infection and REGEN-COV treatment effects.

Conclusions

REGEN-COV treatment appears safe and could prevent disease progression and death in high-risk inpatients with early diagnosis of HA-COVID-19 and underlying illnesses requiring hospital care. A timely diagnosis of HA-COVID-19 – favored by a rigorous infection prevention and control program- and a prompt administration of REGEN-COV could favor the clinical response to treatment. Our promising results need further confirmation by larger, multi-center prospective studies.

Declarations

Author contributions All authors contributed to the study conception and design. Material preparation and data collection were performed by T Picchioni, E Lovicu, G Scocchera, A Lo Forte, A Crociani, P Carrai, S Sbaragli, M Bettucchi. Data analysis was conducted by A Faraone and L Tofani. The first draft of the manuscript was written by A Faraone, F Fabbrizzi and A Fortini and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical standards The study was approved by the institutional review board of the Department of Medicine of the “Azienda USL Toscana Centro”, Florence, Italy. All procedures were performed in accordance with the 1964 Helsinki declaration and its later amendments. Due to the retrospective nature of the study, informed consent was waived according to the applicable local law. Data were de-identified to preserve the anonymity of participants.

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Figures

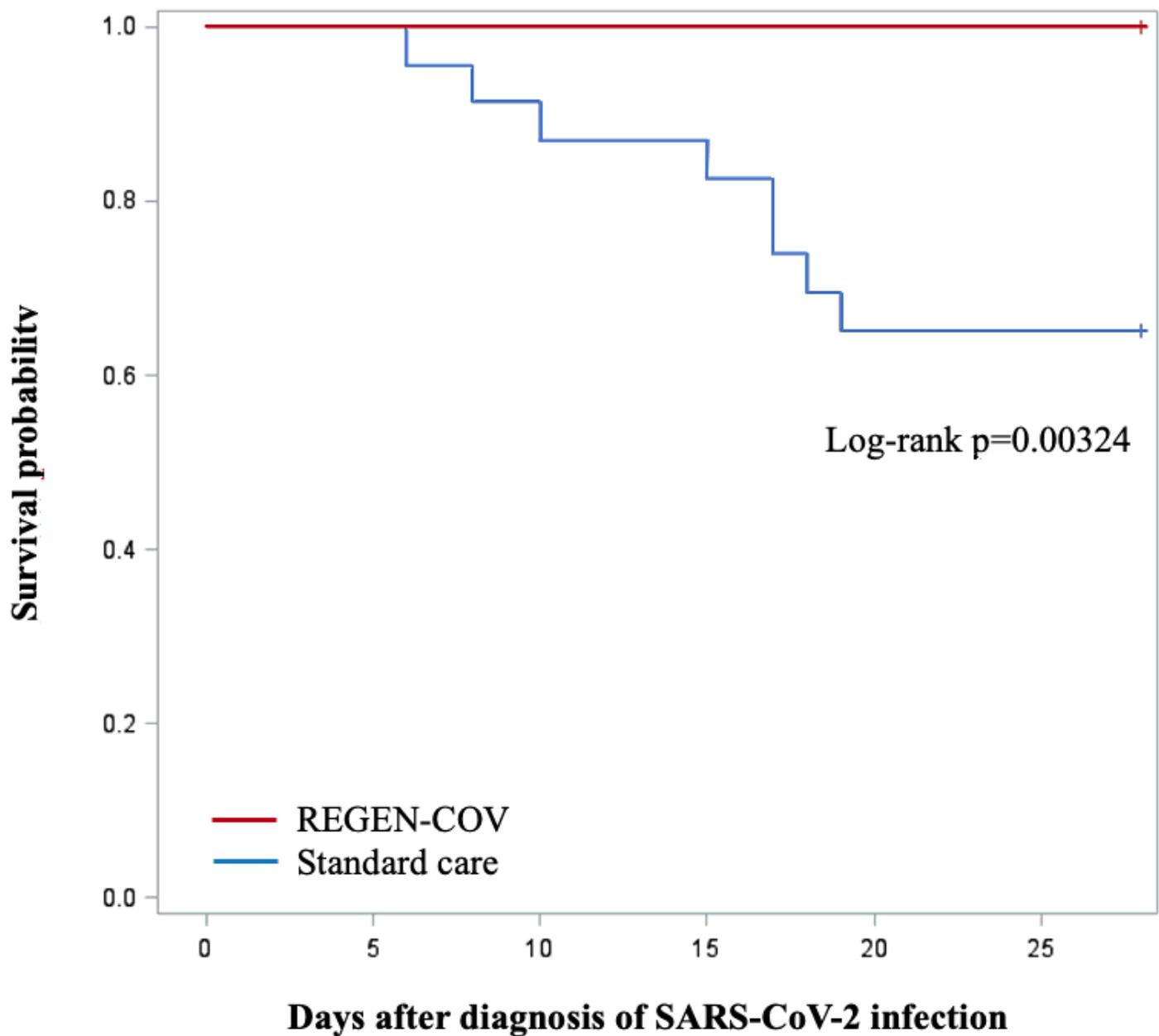


Figure 1

Kaplan-Meier survival curves censored at day 28, according to treatment group (REGEN-COV group vs standard care group). Treatment with REGEN-COV significantly impacted 28-day survival among patients with HA-COVID-19