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# Potential benefit of early treatment with sotrovimab in patients with high risk for severe COVID-19 carrying BA.2 infection

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## ABSTRACT

Coronavirus disease 19 (COVID-19) continues to spread worldwide as a severe pandemic. The Omicron BA.2 became the predominant variant and the protagonist of the ongoing surge. As the virus continues to mutate, using of approved drugs or developing new therapeutic or prophylactic therapies against COVID-19 could be more complex. Sotrovimab is a monoclonal antibody (mAb) targeting the conserved epitope on the spike protein receptor; the most recent studies observed that it has substantially decreased in vitro activity against the Omicron BA.2 subvariant, but real-life data are still scarce. We describe the outcome of a case series of outpatients with BA.1 or BA.2 infection treated with sotrovimab.

We conducted a retrospective observational study including all non-hospitalized adult patients treated with sotrovimab, for which a Sanger sequencing of SARS-CoV-2 was performed within a regional genomic surveillance program.

Eleven (50%) patients with BA.1 infection and eleven (50%) with BA.2 infection were considered. Most patients were immunocompromised. During the follow-up period, no patient died and only one with BA.1 infection was hospitalized for severe COVID-19 pneumonia onset. One month after treatment, 90.9% of patients were completely asymptomatic in each group.

We demonstrated that patients carrying the BA.2 variant treated with sotrovimab did not evolve to severe COVID-19, showing a similar outcome to BA.1 infected patients. Further studies are needed to prove that vaccination or the presumably high doses of mAbs used can protect this group of patients at high risk of progression.

## KEYWORDS

Monoclonal antibodies; Sotrovimab; COVID-19; Omicron; BA.2

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## INTRODUCTION

Late in December 2019 a new SARS-like coronavirus was identified and designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses. The disease related to this virus was named coronavirus disease 19 (COVID-19) by WHO [1,2].

COVID-19 is an ongoing global health emergency and continues to spread worldwide as a severe pandemic. Analysis of SARS-CoV-2 genome sequence has led to an estimated evolutionary rate of approximately $1.1 \times 10^3$ substitutions/site/year [3]. The genomic variations can confer a competitive advantage because of the enhancement of viral replication, viral load, infectivity and immune escape [4].

The Omicron variant (B.1.1.529) was first described in November 2021 in Botswana [5,6]. The initial Omicron variant BA.1 has further evolved and currently, the Omicron variant includes five major sublineages (BA.1-BA.5) [7]. As of February 2022, the BA.2 lineage, has been detected in most countries and has become the predominant variant and the real protagonist of the ongoing surge [8-10]. Differences between BA.1 and BA.2 lineages with other VOCs are consistent: 28 mutations and 50 amino acids make them approximately twice as different compared to the other VOCs diverging from the original wild-type SARS-CoV-2 strain [9,10]. Recently, new sub-variants have appeared that contain identical RBD sequences to BA.2 with the addition of some substitutions, namely BA.2.12.1 (L452Q) and BA.2.13 (L452M) [11].

As the virus continues to mutate mainly in the spike protein, the development, and the approval of therapeutic or prophylactic therapies are currently on the front line of the fight against COVID-19 [12]. Directly-acting antivirals that target viral proteins remain the focus for COVID-19 treatment during the viremic phase because they are directed against viral proteins that are more conserved than the spike, such as the SARS-CoV-2-RNA-dependent RNA polymerase or the -3CL protease [13].

SARS-CoV-2 monoclonal antibodies (mAbs) bind to the receptor-binding domain of the SARS-CoV-2 spike glycoprotein, preventing the viral entry into host cells. The fine specificity of mAbs makes them vulnerable to the emergence of viral variants, thus limiting their effectiveness. Early treatment with mAbs should be considered for non-hospitalized patients with mild to moderate COVID-19 who are not vaccinated or those who are vaccinated but not expected to mount an adequate immune response to the vaccine due to an underlying immunocompromising condition [14] when the available directly-acting antivirals cannot be offered [15].

Since the beginning of the epidemic, a series of mAbs for COVID-19 treatment have been approved: casirivimab/indevimab, bamlanivimab/etesevimab and sotrovimab [16-18]. In general treatment, at an earlier disease stage is a major determinant to achieving protection with mAbs in COVID-19 [19].

Sotrovimab is a mAb targeting the conserved epitope on the spike protein receptor of SARS-CoV-2 and it inhibits a yet undefined step that takes place after the virus attachment and before the fusion of the viral and cell membranes [20]. Sotrovimab was approved by U.S. Food and Drug Administration (FDA) in May 2021 [18] and in Italy in December 2021 [21]; the authorized dosage is one single intravenous infusion of 500 mg [18]. Sotrovimab is indicated for the treatment of mild to moderate COVID-19 in non-hospitalized adults with laboratory-confirmed SARS-CoV-2 infection who are at high risk for progression to severe disease and hospitalization [18,21].

Initially, it was reported that the Omicron variant, which included the BA.1 and BA.1.1 subvariants, was resistant to casirivimab/indevimab and bamlanivimab/etesevimab but remained susceptible to inhibition by sotrovimab [22]. However, the most recent studies observed that sotrovimab has substantially decreased in vitro activity against the Omicron BA.2 subvariant [23,24]. For this reason, in the United States the distribution of sotrovimab has been paused and the National Institutes of Health (NIH) no longer recommends using this mAb to treat COVID-19 [25]. A recent meta-analysis concluded that the use of

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sotrovimab does not have a significant benefit on patients with COVID-19 in either the mortality rate or severity of illness because it is approved in patients with a risk of death very low regardless of the interventions used [26].

Real-life data on the effectiveness of sotrovimab against Omicron variants in non-hospitalized adults with COVID-19 are still scarce. We describe the outcome of a case series of non-hospitalized adults with BA.1 or BA.2 SARS-CoV-2 infection treated with sotrovimab.

## MATERIAL AND METHODS

### *Study population*

We conducted a retrospective observational study including all non-hospitalized adult patients treated with sotrovimab from 1st January until 15th March 2022, for which a Sanger sequencing of SARS-CoV-2 was performed retrospectively within a regional genomic surveillance program.

We treated patients according to the indications provided by Agenzia Italiana del Farmaco (AIFA) [27]. Eligible patients aged 18 years or older and tested positive for SARS-CoV-2 with mild to moderate symptom onset within the prior 7 days. Mild COVID-19 illness is defined by mild symptoms (fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) without dyspnea or abnormal chest imaging, whereas moderate illness is defined by the presence of clinical or radiographic evidence of lower respiratory tract infection with oxygen saturations that exceed 94% [15,28].

They had at least one risk factor for COVID-19 progression among the following: age 65 years or older, diabetes requiring medication, obesity (body mass index >30), chronic kidney disease, chronic liver disease, cardiological disease, bronchopneumopathy [chronic obstructive pulmonary disease (COPD) or severe asthma], solid organ or hematopoietic stem cell transplant, hematological disease, oncological disease or other immunodeficiencies. Patients were excluded if they were hospitalized for COVID-19 pneumonia or if they had signs or symptoms of severe COVID-19.

We describe the effectiveness of sotrovimab-based therapy in terms of persistence of symptoms, time to first negative swab (nasopharyngeal swabs are performed weekly in Italy, per indication of the Ministry of Health [29]), hospitalization and death after one month compared to BA.1 and BA.2 SARS-CoV-2 infection.

This study involving human subjects was performed in accordance with the Helsinki Declaration of 1975 as revised in 2013 and it was approved by the local ethical committee of the Spedali Civili General Hospital of Brescia (approval code NP 5363).

### *Microbiological assays*

- **Detection of SARS-CoV-2 B.1.1.529 variant**

A rapid rise in SARS-CoV-2 B.1.1.529 lineage in Europe prompted the Italian government to implement a genomic surveillance program for SARS-CoV-2-positive samples. Nasopharyngeal specimens were collected at the Brescia Civic Hospital, (Brescia, Lombardy, Italy), using FLOQSwabs in the universal transport medium (UTM) (COPAN, Brescia, Italy). Viral RNA was extracted from 300 µL of UTM with Nimbus automatic system (Arrow Diagnostics, Genoa, Italy), according to the manufacturer's instructions. Amplification was performed on BioRad CFX PCR machine (Bio-Rad Laboratories S.r.l., Milan, Italy) using the Allplex™ 2019-nCoV Assay (Seegene Inc. Seoul, Korea) to evaluate the positivity and the Allplex™ SARS-CoV-2 Variants II Assay to evaluate the presence of the K417N mutation in the S gene. Ct values were automatically calculated using the 2019-CoV Viewer analysis software (Seegene Inc. Seoul, Korea).

- **Viral RNA Extraction and Sanger sequencing**

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The occurrence of BA.1 or BA.2 variant in SARS-CoV-2 K417N samples and the typical spike mutations of the two lineages were examined through Sanger sequencing performed within a regional genomic surveillance program. Total RNA was extracted from 200 µL of PCR-positive nasopharyngeal swabs using QIAamp DSP Virus Kit® (Qiagen, Hilden, Germany) according to the manufacturer's instructions. RNA was eluted in 60 µL of buffer AVE and stored at −80 °C until use. SARS-CoV-2 RNA was reverse-transcribed and PCR amplified using SuperScript™ IV One-Step RT-PCR System with Platinum™ SuperFi DNA Polymerase (Thermo Fisher Scientific, Carlsbad, CA, USA) in a 50 µL reaction containing 25 µL of the reaction mix, 0.5 µL of SuperScriptTM IV RT/PlatinumTM Taq Mix, 2.5 µl of sense and antisense primers (10 µM) and 10 µL of extracted RNA. The amplification conditions were as follows: 55 °C for 10 min (for reverse transcription) and 98 °C for 2 min for DNA polymerase activation, followed by 42 cycles (98 °C for 10 sec, 60 °C for 10 sec, 72 °C for 150 sec) and a final cycle at 72 °C for 5 min. PCR primers used in the reaction were: SARS2-S-F3 (5'-TATCTTGGCAAACCACGCGAACAA) and SARS2-S-R3 (5'-ACCCTTGGAGAGTGCTAGTTGCCATCTC). Afterwards, PCR products were checked on a 1% agarose gel, purified through QIAquick PCR Purification Kit® (Qiagen, Hilden, Germany) and quantified using the Qubit DNA HS Assay Kit (Thermo Fisher Scientific). Then, purified PCR products were sequenced using the SARS2-S-F3 and SARS2-S-R6 (5'-TTCTGCACCAAGTGACATAGTGTAGGCA) primers with the BigDye Terminator v3.1 Cycle Sequencing Kit on SeqStudio Genetic Analyzer (Thermo Fisher Scientific). The derived sequences were analyzed with Geneious software (v.11.1.5) (Biomatters Ltd., Auckland, New Zealand), using the sequence NC_045512.2 as SARS-CoV-2 reference.

**RESULTS**

From 1st January until 15th March 2022, we treated 151 patients with mild/moderate COVID-19 with sotrovimab. Among this populations, the Omicron variant was available for twenty-two patients as part of regional genomic surveillance program.

Eleven (50%) patients showed BA.1 SARS-CoV-2 infection and 11 (50%) BA.2 SARS-CoV-2 infection. The median age was 62 years old, 12 were males (54.5%) and 10 were females (45.5%). Patient characteristics and outcomes are shown in **Table 1**.

In the group of patients affected by BA.1, the median age was 61 years old. Six were males (54.5%) and 5 were females (45.5%). Eight patients (72.7%) received three doses of SARS-CoV-2 vaccine, 2 (18.2%) were unvaccinated. Seven patients (63.6%) showed a mild COVID-19. Regarding the risk of COVID-19 progression, 4 patients (36.4%) were solid organ transplant recipients (three kidney transplants and one hepatic transplant) and 1 patient received a hematopoietic stem cell transplant. Furthermore, 3 (27.3%) patients were on treatment with chemotherapy due to hematological or oncological disease. One had diabetes, one COPD and one had cardiological disease. Among the patients in this group, 5 (45.5%) were affected by chronic renal failure with estimated glomerular filtration rate (eGFR) < 30 ml/min.

In the group of patients affected by BA.2, median age was 63 years old. Six were males (54.5%) and 5 were females (45.5%). Nine patients (81.8%) received three doses of SARS-CoV-2 vaccine, 1 (9.1%) was unvaccinated. Nine patients (81.8%) showed a mild COVID-19. Regarding the risk of COVID-19 progression, 3 patients (27.3%) were renal transplant recipients, and 2 (18.2%) patients were on chemotherapy for hematological or oncological disease. Five patients (45.6%) had severe cardiological impairment. Among patients in this group, 5 (45.5%) were affected by chronic renal failure with eGFR < 30 ml/min and one was affected by chronic liver disease.

The median time between symptoms onset and treatment with sotrovimab was similar for the two groups (4.7 and 4.6 days for BA.1 and BA.2, respectively), as the median time between treatment and SARS-CoV-2 nasal swab negativization (16.6 and 13.4 days for BA.1 and BA.2, respectively).

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During the follow-up period, no patient treated with sotrovimab died and only one with BA.1 SARS-CoV-2 infection was hospitalized 48 hours after therapy for severe COVID-19 pneumonia onset.

One month after treatment, 90.9% of patients were completely asymptomatic in each group. One patient with BA.1 reported persistence of headache, while one patient with BA.2 reported persistence of exertional dyspnea.

**DISCUSSION**

In this retrospective study the outcome of early treatment with sotrovimab in outpatients with COVID-19 who are at high risk of becoming seriously ill, was similar for BA.1 or BA.2 infection, with optimal clinical and virological benefits. Noteworthy, three transplant recipient patients infected with the BA.2 variant and treated with sotrovimab, did not evolve to a severe form of COVID-19 and within one month after treatment became asymptomatic and cleared SARS-CoV-2 infection. Because immunosuppression may impair the adequate production of protective antibodies after vaccination, the use of external mAbs may be more indicated in transplant recipients, known to be at high risk for COVID-19 poor outcomes.
There are few studies regarding the beneficial use of sotrovimab in real life settings during the Omicron era [30,31]; a recent study by Izumo et al. demonstrated a positive outcome in high-risk patients treated with sotrovimab, both in vaccinated and unvaccinated patients [31].

Omicron is a highly transmissible variant of SARS-CoV-2, and it has caused the biggest surge in COVID-19 cases in many countries so far. Omicron is continuously evolving after the initially identified BA.1, BA.1.1, and BA.2, new sub-variants have been identified in the last weeks. Currently, the BA.2 subvariant represents most of all the Omicron cases globally [8]. Countries are facing a new scenario where patients who received complete vaccination with current mRNA vaccines show a substantial loss in neutralizing activity against Omicron variants, becoming again susceptible to infection [23,32].

Several directly-acting antiviral drugs that are currently used in clinical practice for the early treatment of outpatients with COVID-19 who are at the highest risk of becoming seriously ill (remdesivir, molnupinavir and nirmatrelvir) have proven to be effective against the "stealth" BA.2 Omicron variant [24].
Remdesivir and nirmatrelvir were able to reduce the risk of illness progression with very similar capacity (80-90%), but their prescription has some limitations [24]. An alternative is represented by SARS-CoV-2 mAbs but the cumulative mutations on Omicron variants have rendered many of the approved mAbs ineffective [32]. Furthermore, as sotrovimab targets a single epitope on the spike protein, the risk of developing treatment-resistance mutations is not negligible. A recent study by Vellas et al. showed *in vivo* that sotrovimab exposure induces the emergence of omicron-variants harboring mutations and a significant increase in the virus complexity seven days post-infusion [33].

BA.2 exhibits significant *in vitro* resistance to most of the neutralizing monoclonal antibodies approved, including sotrovimab [23, 34]. Sotrovimab has a 77-fold increase in the IC 50 against BA.2 vs only 7.8-fold for BA.1. The current dose of sotrovimab (500 mg) is predicted to provide only 19.3% protection against progression from symptomatic Omicron BA.2 infection to hospitalization [19].
The same authors integrating data from more than 30 randomized controlled trials suggest that the dose of mAbs required to prevent progression from mild to severe disease is up to 1000-fold lower than many current treatment regimens [19].

SARS-CoV-2 deep sequencing is not routinely done to guide clinical practice but to monitor variants worldwide. From April 5, 2022 sotrovimab is no longer authorized to treat COVID-19 in any U.S. region due

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to the increase of COVID-19 cases caused by the Omicron BA.2 sub-variant [35]. In the European region, sotrovimab is not contraindicated despite the predominance of the circulating BA.2 variant.

In this study, we demonstrated that patients carrying the BA.2 variant treated with sotrovimab did not evolve to severe COVID-19. Whether vaccination or the presumably high doses of mAb used can protect this group of patients at high risk of progression, even against not completely sensitive variants, remains to be investigated. The emergence of new variants is narrowing our treatment options and challenging the effectiveness of current vaccines. Fortunately, directly-acting antiviral drugs seem to retain efficacy against the new SARS-CoV-2 variants while more treatments are being developed.

**Author Contributions**

E.Q.-R.: Conceptualization; E.Q.-R., C.G. and M.D.A.: Original Draft Preparation; M.D.A., C.G, S.M., S.A., F.C., F.C., A.C. and E.Q.-R.: Methodology, Software, Validation, Investigation, Resources, Data Curation, Writing—Review & Editing, Visualization, Supervision. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest**

The authors declare no conflict of interest.

**Ethics approval**

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of or Hospital.

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**Table 1. Patients' characteristics and outcomes.**

| N. | Sex | Age | SARS-CoV-2 Vaccine doses | Risk factor for COVID-19 progression | SARS-CoV-2 variant | COVID-19 severity | Time between symptoms onset and treatment, days. | Outcome at 1 month | Time between treatment and SARS-CoV-2 nasal swab negativization, days. | Time between SARS-CoV-2 nasal swab positivization and nasal swab negativization, days. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 68 | 3 | Kidney transplantation<br>Chronic renal failure | B.1.1.529 BA.1 | Moderate | 4 | Hospitalized for COVID-19 | 27 | 29 |
| 2 | F | 61 | 2 | Kidney transplantation<br>Chronic renal failure<br>Cardiological disease<br>Obesity | B.1.1.529 BA.1 | Moderate | 7 | Alive, asymptomatic | 12 | 14 |
| 3 | F | 60 | 3 | Kidney transplantation<br>Chronic renal failure | B.1.1.529 BA.1 | Mild | 3 | Alive, asymptomatic | 6 | 8 |
| 4 | M | 75 | 3 | Hepatic transplantation<br>Chronic renal failure | B.1.1.529 BA.1 | Mild | 6 | Alive, asymptomatic | 23 | 27 |
| 5 | M | 84 | 3 | Chronic renal failure<br>Cardiological disease | B.1.1.529 BA.1 | Mild | 3 | Alive, symptomatic* | 12 | 14 |
| 6 | F | 43 | 3 | Oncological disease[1] | B.1.1.529 BA.1 | Mild | 5 | Alive, asymptomatic | 14 | 15 |
| 7 | F | 40 | 0 | Haematopoietic stem cell transplantation | B.1.1.529 BA.1 | Moderate | 3 | Alive, asymptomatic | 10 | 13 |
| 8 | F | 64 | 3 | Hematological disease[2]<br>Cardiological disease | B.1.1.529 BA.1 | Mild | 7 | Alive, asymptomatic | 18 | 22 |
| 9 | M | 58 | 3 | Hematological disease[2] | B.1.1.529 BA.1 | Mild | 2 | Alive, asymptomatic | 21 | 28 |
| 10 | M | 66 | 0 | Diabetes requiring medication | B.1.1.529 BA.1 | Mild | 5 | Alive, asymptomatic | 12 | 16 |
| 11 | M | 55 | 3 | COPD<br>Obesity | B.1.1.529 BA.1 | Moderate | 7 | Alive, asymptomatic | 27 | 35 |

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|---|---|---|---|---|---|---|---|---|---|---|
| 12 | M | 44 | 3 | Kidney transplantation<br>Chronic renal failure | B.1.1.529 BA.2 | Mild | 6 | Alive, asymptomatic | 11 | 14 |
| 13 | M | 59 | 3 | Kidney transplantation<br>Chronic renal failure | B.1.1.529 BA.2 | Mild | 2 | Alive, asymptomatic | 20 | 21 |
| 14 | F | 74 | 3 | Kidney transplantation<br>Chronic renal failure | B.1.1.529 BA.2 | Mild | 6 | Alive, asymptomatic | 12 | 15 |
| 15 | F | 67 | 3 | Oncological disease[3] | B.1.1.529 BA.2 | Moderate | 6 | Alive, asymptomatic | 8 | 14 |
| 16 | F | 78 | 3 | Hematological disease[4] | B.1.1.529 BA.2 | Mild | 3 | Alive, asymptomatic | 19 | 22 |
| 17 | M | 73 | 2 | Cardiological disease | B.1.1.529 BA.2 | Mild | 6 | Alive, asymptomatic | 4 | 7 |
| 18 | M | 48 | 3 | Cardiological disease<br>Obesity | B.1.1.529 BA.2 | Mild | 3 | Alive, asymptomatic | 10 | 13 |
| 19 | F | 36 | 3 | Cardiological disease<br>Chronic liver disease | B.1.1.529 BA.2 | Moderate | 6 | Alive, symptomatic[§] | 12 | 18 |
| 20 | M | 81 | 3 | Cardiological disease<br>Diabetes requiring medication<br>Chronic renal failure | B.1.1.529 BA.2 | Mild | 6 | Alive, asymptomatic | 7 | 13 |
| 21 | F | 82 | 3 | Cardiological disease | B.1.1.529 BA.2 | Mild | 4 | Alive, asymptomatic | 22 | 26 |
| 22 | M | 46 | 0 | Immunodeficiency<br>Chronic renal failure | B.1.1.529 BA.2 | Mild | 2 | Alive, asymptomatic | 22 | 26 |

[1] Breast cancer, ongoing chemotherapy

[2] Chronic lymphocytic leukemia; ongoing chemotherapy

[3]Lung cancer; ongoing chemotherapy

[4]Multiple myeloma; ongoing chemotherapy

[5] Schoenlein Henoch Syndrome; ongoing immunosoppressive therapy

*Persistence of headache

[§]Persistence of exertional dyspnea

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