Letters

RESEARCH LETTER

Development of Resistance-Associated Mutations After Sotrovimab Administration in High-risk Individuals Infected With the SARS-CoV-2 Omicron Variant

The SARS-CoV-2 Omicron variant of concern is currently the dominant variant circulating globally. Sotrovimab is among the few monoclonal antibodies that has retained its neutralizing activity against Omicron/BA.1 and received Emergency Use Authorization for treatment of patients at risk for progression to severe disease.[1,2]

Supplemental content

However, concerns have been raised about the potential induction of spike protein resistance-associated viral mutations, especially in immunocompromised patients who are at risk for prolonged infection with SARS-CoV-2.[3] We investigated whether resistance-associated mutations developed after treatment with sotrovimab in high-risk patients infected with the SARS-CoV-2 Omicron variant.

Methods | During the study period (January-February 2022), a single 500-mg dose of sotrovimab was recommended for use in ambulatory and hospitalized high-risk patients with SARS-CoV-2 infection. All patients treated at Amsterdam University Medical Centers in the Netherlands were eligible. The study was approved by the medical ethical committee for the Amsterdam University Medical Centers. Included patients provided written informed consent.

Nasopharyngeal specimens were prospectively collected on days 0, 7, and 28 (at the discretion of the clinicians, additional specimens were collected 4 days before the sotrovimab infusion [4 days before day 0] to day 52). Specimens were selected for whole-genome sequencing (Nanopore sequencing; Oxford Nanopore Technologies) if the cycle threshold value was 34 or less. The phylogenetic relationship of the obtained specimens was compared with nearly 5000 sequences from randomly selected samples from the Amsterdam region obtained as part of routine genomic surveillance (eMethods in the Supplement).

The primary outcome was the emergence of spike protein resistance-associated mutations at position E340 or P337 during treatment. A Cox proportional hazard model was used for the analysis of time to viral clearance with mutation as a covariate (eMethods in the Supplement). The statistical analysis was conducted using RStudio version 4.1 (RStudio). A 2-tailed threshold of $P<.05$ defined statistical significance.

Results | Of 47 high-risk patients with COVID-19 administered sotrovimab during the study period, 18 had more than 1 specimen and were included in the study (13 declined, 7 were unable to be reached, 8 were lost to follow-up, and 1 died before second specimen collection). The mean age of the patients was 60.9 years (SD, 15.2 years), 9 (50%) were female, and 15 (83%) were immunocompromised due to underlying conditions or use of an immunosuppressive medication (**Table**). Specimens were collected at all 3 time points from 14 of the 18 patients (78%). Patients received an infusion with sotrovimab between 0 and 23 days after a positive reverse transcriptase-polymerase chain reaction test result for SARS-CoV-2 and were enrolled in the study within 2 days of the infusion.

Genomic analysis revealed that all 18 (100%) patients were infected with the Omicron variant; 17 with BA.1 (94%) and 1 with BA.2 (6%). Ten patients (56%) developed receptor-binding domain mutations at spike position E340 or P337 within 3 to 31 days

Table. Baseline Demographics and Clinical Characteristics of Patients Treated With Sotrovimab (N = 18)

	Patients, No. (%)[a]
Demographics	
Age, mean (SD), y	60.9 (15.2)
Sex	
Female	9 (50.0)
Male	9 (50.0)
Body mass index, median (IQR)[b]	24.2 (22.8-25.4)
Clinical characteristics	
Symptomatic	17 (94.4)
Time between start of symptoms and treatment with sotrovimab, median (IQR), d	4 (2-9)
Time between first positive RT-PCR and treatment with sotrovimab, median (IQR), d	1 (0.3-2)
Cycle threshold value of positive RT-PCR, median (IQR)	23 (20.8-27)
Fully vaccinated (2 doses and 1 booster dose)	13 (72.2)
SARS-CoV-2 seronegative (antibodies negative)	16 (88.9)
SARS-CoV-2 antibody status unknown	2 (11.1)
Administration of sotrovimab during hospitalization	4 (22.2)

(continued)

Table. Baseline Demographics and Clinical Characteristics of Patients Treated With Sotrovimab (N = 18) (continued)

	Patients, No. (%)[a]
Comorbidities	
Underlying immunosuppressive conditions[c]	15 (83.3)
Hematological malignancy	5 (27.8)
Chronic lymphocytic leukemia	1 (5.6)
Multiple myeloma	2 (11.1)
Diffuse large B-cell lymphoma	1 (5.6)
Epstein-Barr virus–associated lymphoma	1 (5.6)
Solid malignancy	1 (5.6)
Rheumatic diseases	5 (27.8)
Systemic lupus erythematosus	1 (5.6)
Rheumatoid arthritis	4 (22.2)
Solid organ transplant (2 kidney recipients and 1 kidney and lung recipient)	3 (16.7)
Autologous stem cell transplant	3 (16.7)
Common variable immunodeficiency	1 (5.6)
Immunosuppressive medication	
Any immunosuppressive medication	13 (72.2)
Corticosteroids	9 (50.0)
B- or T-cell inhibitors[d]	7 (38.9)
Chemotherapy[e]	4 (22.2)
Other[f]	6 (33.3)
Outcomes	
Hospitalized for COVID-19[g]	5 (27.8)
Length of hospital stay, median (IQR), d	8 (4-10)
Any type of oxygen therapy	5 (27.8)
High-flow oxygen therapy[h]	4 (22.2)
Low-flow oxygen therapy[i]	1 (5.6)
Intensive care unit admission	1 (5.6)
30-d mortality due to treatment-resistant COVID-19	1 (5.6)

Abbreviation: RT-PCR, reverse transcriptase–polymerase chain reaction.

[a] Unless otherwise indicated.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Or use of an immunosuppressive medication for 3 months or less before treatment with sotrovimab.

[d] Azathioprine, belatacept, leflunomide, mycophenolate mofetil, mycophenolic acid, tacrolimus, or rituximab.

[e] Capecitabine or cyclophosphamide.

[f] Lenalidomide, methotrexate, iberdomide, hydroxycarbamide, or hydroxychloroquine.

[g] Treated with supplemental oxygen, dexamethasone, and the anti–IL-6 receptor antagonist sarilumab.

[h] Nonrebreather mask or high-flow nasal cannula.

[i] Face mask or low-flow nasal cannula.

after treatment. No S:E340 or S:P337 mutations were found in the Omicron variant from the sequences from the general population (**Figure**). We identified 6 mutations in S:E340K/A/V/D/G/Q and 3 in S:P337L/R/S. Mutations increased over time and exceeded 50% between day 5 and day 28. Patients with mutations had significantly delayed time to viral clearance (mean, 32 [SD, 8.1] days vs 19.6 [SD, 11.1] days for those without mutations); hazard ratio, 0.11 [95% CI, 0.02-0.60]). The 4 patients with the sotrovimab resistance–associated S:E340K mutation were immunocompromised.

Discussion | This study found rapid development of sotrovimab resistance–associated mutations at positions S:E340 and S:P337 in a large proportion of high-risk patients infected with the Omicron variant after treatment with sotrovimab, which was associated with a delay in viral clearance. These results are in line with a report describing the occurrence of resistance mutations 6 to 13 days after treatment with sotrovimab in patients infected with the Delta variant.[4]

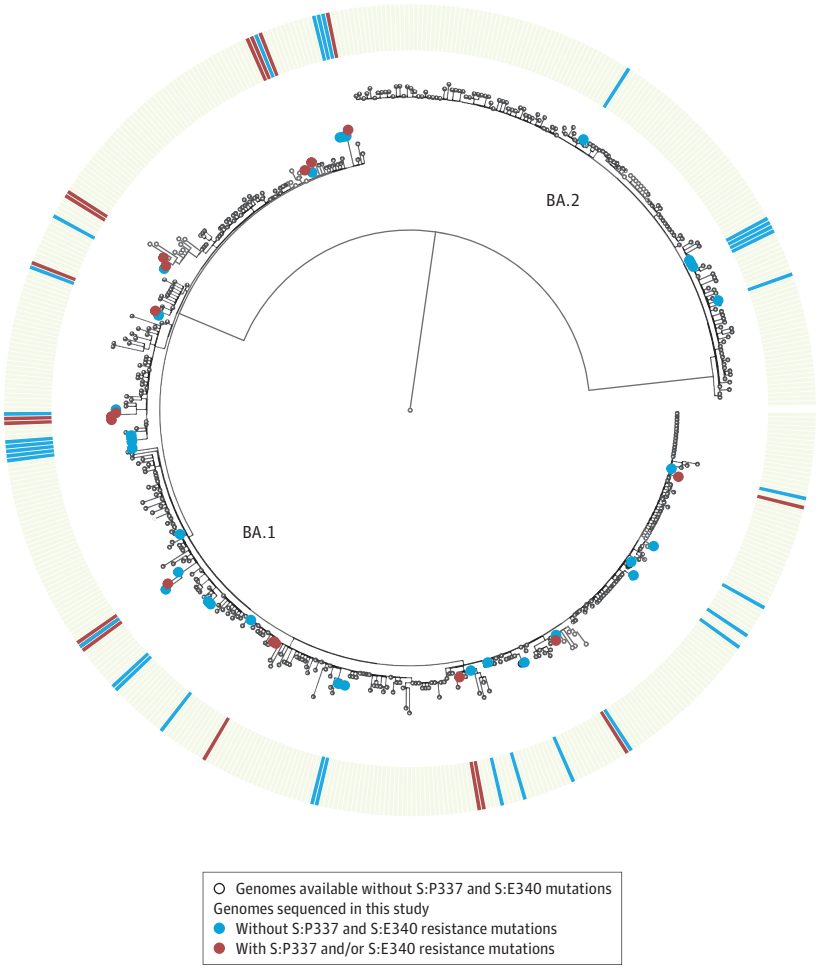
Spike protein mutations at positions S:E340K/A/V/G and S:P337L/R have been associated with a 27- to 279-fold reduction in susceptibility to sotrovimab.[4,5] The present findings add to the emerging evidence that treatment of high-risk patients with a single monoclonal antibody is associated with mutation development, especially in immunocompromised patients who are at risk for prolonged infection.[3,4]

Study limitations include a relatively small sample size, possible sampling or nonresponse bias, lack of a control group, technical restrictions of the sequencing platform, and lack of clinical outcomes. Further studies investigating combination monoclonal antibody therapy and continuous genomic surveillance in immunocompromised patients are warranted to address the expanding antigenic diversity and subsequent emergence of resistance during COVID-19 treatment.

Emma Birnie, MD, PhD
Jason J. Biemond, MD
Brent Appelman, MD
Godelieve J. de Bree, MD, PhD
Marcel Jonges, PhD
Matthijs R. A. Welkers, MD, PhD
W. Joost Wiersinga, MD, PhD

Author Affiliations: Center for Experimental and Molecular Medicine, Amsterdam University Medical Centers, Amsterdam, the Netherlands (Birnie, Biemond, Appelman, Wiersinga); Division of Infectious Diseases, Amsterdam University Medical Centers, Amsterdam, the Netherlands (de Bree); Department of Medical Microbiology and Infection Prevention, Amsterdam University Medical Centers, Amsterdam, the Netherlands (Jonges, Welkers).

Figure. Emergence and Phylogenetic Relationship of Sotrovimab-Associated Resistance Mutations in the SARS-CoV-2 Omicron Variant After Treatment With Sotrovimab



Omicron BA.1 and BA.2 variants were found in 18 patients. Ten patients (56%) developed S:E340 and/or S:P337 resistance mutations. No S:E340 or S:P337 mutations were found in the Omicron variant outside the study population. Phylogenetic tree is rooted to Hu-1.

Accepted for Publication: July 25, 2022.

Published Online: August 1, 2022. doi:10.1001/jama.2022.13854

Corresponding Author: Emma Birnie, MD, PhD, Center for Experimental and Molecular Medicine, Meibergdreef 9, Amsterdam, the Netherlands (e.birnie@amsterdamumc.nl).

Author Contributions: Drs Birnie and Wiersinga had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Birnie and Biemond contributed equally.
Concept and design: Birnie, de Bree, Welkers, Wiersinga.
Acquisition, analysis, or interpretation of data: Birnie, Biemond, Appelman, Jonges, Welkers, Wiersinga.
Drafting of the manuscript: Birnie, Biemond, Welkers, Wiersinga.
Critical revision of the manuscript for important intellectual content: Birnie, Biemond, Appelman, Jonges, Welkers, Wiersinga.
Statistical analysis: Birnie, Biemond, Welkers.
Obtained funding: de Bree, Wiersinga.
Administrative, technical, or material support: Birnie, Biemond, Appelman, Jonges, Welkers.
Supervision: Birnie, Wiersinga.

Conflict of Interest Disclosures: Dr Wiersinga reported receiving grant support (grant 91716475) from the Netherlands Organization of Scientific Research and personal fees (fees paid to his institution) from GlaxoSmithKline, Pfizer, Sobi, and AstraZeneca. No other disclosures were reported.

Funding/Support: This study was funded by grant 10430142110001 from the Netherlands Organization for Health Research and Development.

Role of the Funder/Sponsor: The Netherlands Organization for Health Research and Development had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the physicians, nurses, and other health care clinicians at the Amsterdam University Medical Centers and all the patients who participated in this study. The research presented is part of a Dutch cohort study on neutralizing monoclonal antibodies against and other antiviral agents against SARS-CoV-2 (TURN-COVID; NCT05195060). Additional contributions appear in the Supplement.

1. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19). *JAMA*. 2020;324(8):782-793.

2. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of sotrovimab on hospitalization or death among high-risk patients with mild to moderate COVID-19. *JAMA*. 2022;327(13):1236-1246.

3. Corey L, Beyrer C, Cohen MS, et al. SARS-CoV-2 variants in patients with immunosuppression. *N Engl J Med*. 2021;385(6):562-566.

4. Rockett R, Basile K, Maddocks S, et al. Resistance mutations in SARS-CoV-2 Delta variant after sotrovimab use. *N Engl J Med*. 2022;386(15):1477-1479.

5. Cameroni E, Bowen JE, Rosen LE, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. *Nature*. 2022;602(7898):664-670.