CORRESPONDENCE

Resistance Mutations in SARS-CoV-2 Delta Variant after Sotrovimab Use

TO THE EDITOR: Sotrovimab is a monoclonal antibody that is available under emergency use authorization for the treatment of patients who are at risk for progression of coronavirus disease 2019 (Covid-19) to severe disease.[1] Sotrovimab is thought to neutralize all sarbecoviruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), by binding to a highly conserved epitope within the receptor-binding domain.[2] However, the use of SARS-CoV-2–specific monoclonal antibodies to target a single viral epitope warrants caution because of the risk of rapid development of mutations that confer resistance after exposure to these antibodies.[2-4] Mutations at positions S:E340K/A/V and S:P337L/T (Fig. 1A) have been associated with a reduction by a factor of 100 to 297 in neutralization by sotrovimab.[5]

We reviewed the first 100 consecutive patients who received sotrovimab at health care facilities in the Western Sydney Local Health District in New South Wales, Australia, during the B.1.617.2 (delta) variant outbreak between August and November 2021 (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). We identified 8 patients (Patients R001 through R008) with reverse transcriptase–polymerase-chain-reaction (RT-PCR) assays that were persistently positive for SARS-CoV-2 and for whom respiratory tract specimens obtained before and after the use of sotrovimab were available.

Genomic analysis showed that 4 of these 8 patients (Patients R001 through R004) acquired previously defined receptor-binding domain mutations within 6 to 13 days after they received sotrovimab (Fig. 1C and Table S1). Mutations in S:E340 developed in all 4 patients, findings that are concordant with those in the Covid-19 Monoclonal Antibody Efficacy Trial–Intent to Care Early (COMET-ICE).[2] Cultures obtained from these patients remained positive for 23, 24, 12, and 15 days, respectively, after they received sotrovimab (Table S2). Read frequencies of S:E340K/A/V mutations increased over the course of infection; the proportion of the viral population carrying S:E340K/A/V exceeded 75% by day 7 in Patient R002, by day 13 in Patient R003, and by day 37 in Patient R004 (Fig. 1C and Table S2). In addition, a minority variant developed in Patient R002 at position P337L after fixation of the S:E340K mutation. A retrospective review of 11,841 SARS-CoV-2 genomes in the Global Initiative on Sharing All Influenza Data database (a site for compiling sequence data on viruses) (Table S3) and reported in New South Wales, Australia, identified 4 additional patients with S:E340 mutations. In 1 patient, the SARS-CoV-2 genome was detected 5 days after sotrovimab treatment, and in another it was detected 11 days after treatment.

These data show the persistence of viable SARS-CoV-2 in patients after sotrovimab infusions and the rapid development of spike gene mutations associated with high-level sotrovimab resistance in vitro. These findings underscore the importance of stewardship of monoclonal antibodies, particularly because sotrovimab is one of the few monoclonal antibodies with retained activity against the B.1.1.529 (omicron) variant.[1] Postmarketing genomic surveillance of patients who receive monoclonal antibodies for the treatment of SARS-CoV-2 infection is prudent in order to minimize the risk of both treatment failure and the transmission of potentially resistant SARS-CoV-2 variants in health care settings and the community, given that SARS-CoV-2 may be isolated up to 24 days after sotrovimab treatment.

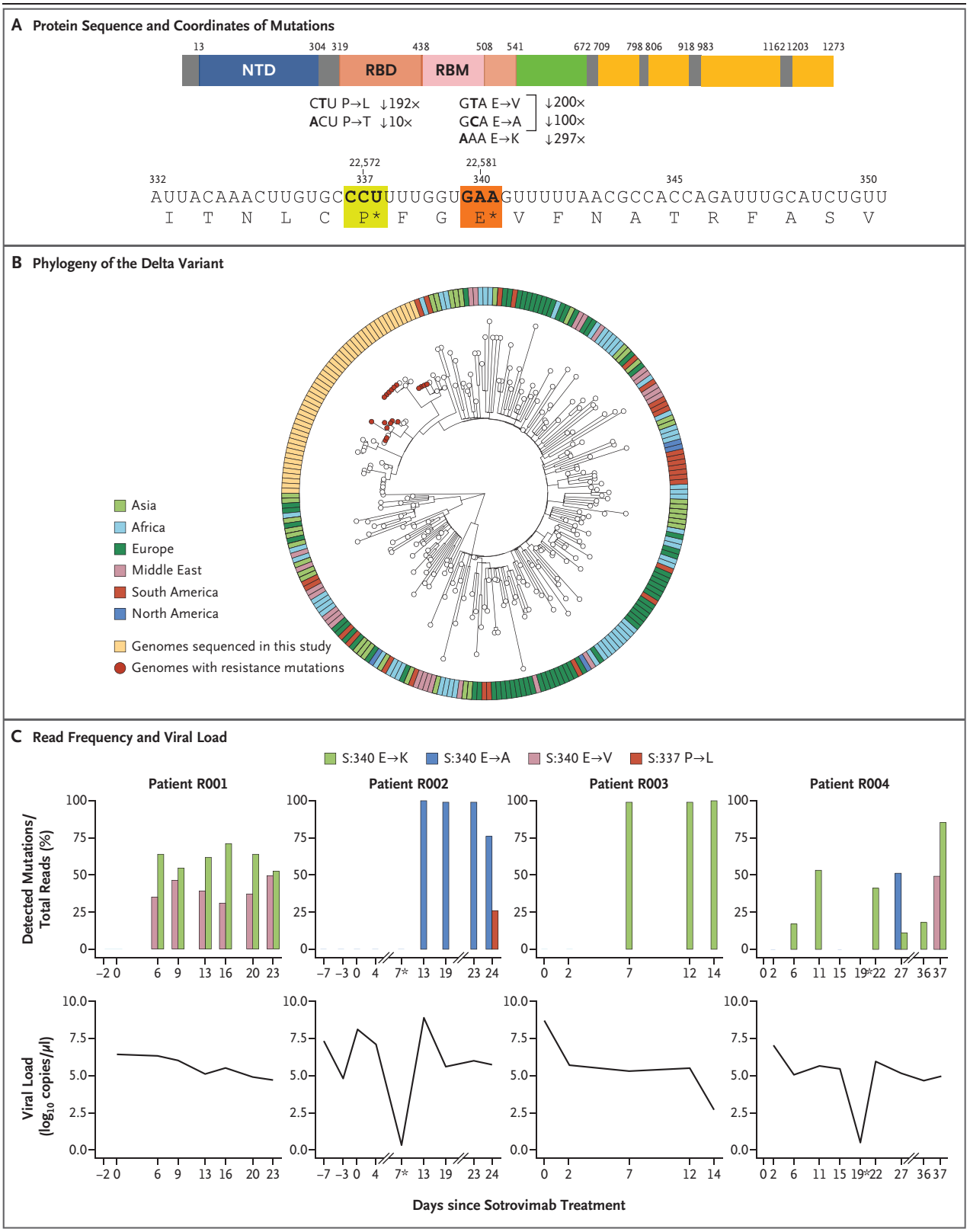
A Protein Sequence and Coordinates of Mutations
13
304 319
438
508 541
672 709
798 806
918 983
1162 1203
1273
NTD
RBD
RBM
CTU P→L ↓192×
ACU P→T ↓10×
GTA E→V
GCA E→A
AAA E→K
↓200×
↓100×
↓297×
22,572
22,581
332
337
340
345
350
AUUACAAACUUGUGCCCUUUUGGUGAAGUUUUUAACGCCACCAGAUUUGCAUCUGUU
I T N L C P* F G E* V F N A T R F A S V
B Phylogeny of the Delta Variant
Asia
Africa
Europe
Middle East
South America
North America
Genomes sequenced in this study
Genomes with resistance mutations
C Read Frequency and Viral Load
S:340 E→K
S:340 E→A
S:340 E→V
S:337 P→L
Patient R001
Patient R002
Patient R003
Patient R004
Detected Mutations/ Total Reads (%)
Viral Load (log10 copies/μl)
Days since Sotrovimab Treatment

Figure 1 (facing page). SARS-CoV-2 Viral-Load Dynamics and Acquisition of Resistance Mutations after Sotrovimab Treatment.

The acquisition of mutations conferring a high level of resistance to sotrovimab and the dynamics of the viral load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are shown. Panel A shows the N-terminal domain (NTD), receptor-binding domain (RBD), and receptor-binding motif (RBM) of the SARS-CoV-2 spike protein and the protein sequence and coordinates of mutations that were acquired in the RBD of the spike protein after sotrovimab treatment. We found five mutations (S:E340K/A/V and S:P337L/T) that have been reported to reduce susceptibility to sotrovimab by factors of 297, 100, 200, 192, and 10, respectively.[1,5] Panel B shows the global phylogeny of subsampled isolates of the SARS-CoV-2 delta variant, a variant of concern, with the geographic region of sequences indicated in the outer ring. Panel C shows the findings in four patients with SARS-CoV-2 infection who received sotrovimab. The acquisition and read frequency of mutations conferring high levels of resistance to sotrovimab and the SARS-CoV-2 load at each sampling point are shown. The asterisks indicate two sampling time points in which a high-quality SARS-CoV-2 genome could not be recovered (in Patient R002 on day 7 and in Patient R004 on day 19) and potential resistance mutations could not be revealed. All the patients in whom resistance mutations developed (Patients R001 through R004) were hospitalized during the sampling periods.

Rebecca Rockett, Ph.D.
University of Sydney
Sydney, NSW, Australia
rebecca.rockett@sydney.edu.au

Kerri Basile, M.D.
NSW Health Pathology
Sydney, NSW, Australia

Susan Maddocks, M.D., Ph.D.
Winkie Fong, Ph.D.
Western Sydney Local Health District
Westmead, NSW, Australia

Jessica E. Agius, Ph.D.
Jessica Johnson-Mackinnon, Ph.D.
University of Sydney
Sydney, NSW, Australia

Alicia Arnott, Ph.D.
NSW Health Pathology
Sydney, NSW, Australia

Shona Chandra, Ph.D.
Western Sydney Local Health District
Westmead, NSW, Australia

Mailie Gall, Ph.D.
Jenny Draper, Ph.D.
Elena Martinez, Ph.D.
Eby M. Sim, Ph.D.
Clement Lee, B.S.
Christine Ngo, B.S.
Marc Ramsperger, Ph.D.
Andrew N. Ginn, Ph.D.
Qinning Wang, Ph.D.
Michael Fennell, M.S.
Danny Ko, B.S.
NSW Health Pathology
Sydney, NSW, Australia

H. Ling Lim, M.D.
Nicky Gilroy, M.D.
Western Sydney Local Health District
Westmead, NSW, Australia

Matthew V.N. O'Sullivan, M.D., Ph.D.
Sharon C.-A. Chen, M.D., Ph.D.
Jen Kok, M.D., Ph.D.
Dominic E. Dwyer, M.D.
NSW Health Pathology
Sydney, NSW, Australia

Vitali Sintchenko, M.D., Ph.D.
University of Sydney
Sydney, NSW, Australia
vitali.sintchenko@sydney.edu.au

Supported by the Prevention Research Support Program, which is funded by the New South Wales (NSW) Ministry of Health; NSW Health Covid-19 priority funding; a grant (APPRISE 1116530) from the National Health and Medical Research Council, Australia; and a Jerry Koutts Ph.D. Scholarship (to Dr. Basile) from the Institute of Clinical Pathology and Medical Research.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on March 9, 2022, at NEJM.org.

1. Cameroni E, Bowen JE, Rosen LE, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 omicron antigenic shift. Nature 2022;602:664-70.
2. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med 2021;385:1941-50.
3. Chen RE, Zhang X, Case JB, et al. Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. Nat Med 2021;27:717-26.
4. Choi B, Choudhary MC, Regan J, et al. Persistence and evolution of SARS-CoV-2 in an immunocompromised host. N Engl J Med 2020;383:2291-3.
5. Cathcart AL, Havenar-Daughton C, Lempp FA, et al. The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2. March 10, 2021 (https://www.biorxiv.org/content/10.1101/2021.03.09.434607v1). preprint.

DOI: 10.1056/NEJMc2120219