

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.