Sotrovimab resistance and viral persistence after treatment of immunocompromised patients infected with the SARS-CoV-2 Omicron variant

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Running title: Sotrovimab resistance in Omicron patients

Abstract

Viral evolution was evaluated in 47 immunocompromised patients treated with sotrovimab. Sequencing of SARS-CoV-2 following therapy was successful in 16. Mutations associated with sotrovimab resistance were documented in 6, viral replication continued after 30 days in 5. Combination antibody therapy may be required to avoid acquired resistance in immunocompromised patients.

Keywords: SARS-CoV-2, Omicron, sotrovimab, resistance, immunocompromised

Introduction

Sotrovimab is a monoclonal antibody that neutralizes SARS-CoV-2 by binding to a highly conserved epitope in the receptor binding domain of sarbecoviruses. It was one of the few approved monoclonals that retained activity against the Omicron BA.1 variant of concern (VOC).[1] While its activity against Omicron BA.2 is limited, emerging data suggest it may again be useful to treat the most recent Omicron subvariants BA.2.12.1, BA 4 and 5.[2, 3]

Immunocompromised patients are at an increased risk for a severe outcome of COVID-19 even after full vaccination against SARS-CoV-2. Indeed, the vaccination response is often reduced and can be completely absent in patients with combined T-cell and B-cell dysfunction.[4, 5] Furthermore, prolonged viral replication and evolution have been described in the immunocompromised host.[6, 7] Given the risk for a poor outcome, monoclonal antibody-based therapy is frequently used to treat these patients. Viral evolution towards resistance against these monoclonal antibodies can arise when viral replication is not sufficiently contained, and this risk may be more pronounced during antibody *mono*therapy. Recently, the selection of mutations in the Spike protein of the Delta VOC in 4 of 100 patients treated with sotrovimab was reported and all 4 were immunocompromised.[8] Specifically, mutations were found at position 337 and 340, known to reduce susceptibility to sotrovimab.[9] We studied viral evolution in 47 immunocompromised patients treated with sotrovimab for an infection with the Omicron VOC.

Methods

At the Erasmus University Medical Center in Rotterdam, sotrovimab became available on January 26th, 2022. It was used to treat immunocompromised patients infected with the SARS-CoV-2 Omicron VOC in the outpatient and inpatient setting. Before treatment, patients were screened for the presence of SARS-CoV-2 antibodies using the LIAISON® SARS-CoV-2 TrimericS IgG assay (DiaSorin). A SARS-CoV-2 PCR was performed at baseline and weekly thereafter, also after discharge until the PCR Cyclic threshold (Ct)-value was ≥30.[10] Baseline and follow-up samples with a Ct-value <30 were sequenced on the Nanopore platform. Successful sequencing was defined as at least 90% of the genome covered with at

least 30x coverage. Only descriptive statistics were used. The study was approved by the institutional review board under number METC2021-0309.

Results

Of the 47 patients treated, 24 (51%) were male, the median age was 63 (IQR 51 – 67), 31 (66%) had undergone an organ transplantation. Seventeen patients (36%) received triple immunosuppressive therapy (mycophenolic acid, calcineurin inhibitors and corticosteroids) as anti-rejection drugs after solid organ transplant, 10 patients (21%) received anti-CD20 agents and thus B-cell depleting therapy. 32 of 47 (68%) patients were hospitalized for their COVID-19 infection and were treated with sotrovimab on the COVID-ward. Information on IgG Spike antibody titers in the 30 days preceding sotrovimab therapy was available for 36 patients. Spike antibodies were negative in 22 (61%) and very low (1-300 BAU/mL) in 9 (25%). These low or negative antibody titers were observed despite a history of at least 2 mRNA vaccinations in 30/36 (83%) patients and 3 vaccinations or more in 24/36 (66%) patients. We refer to supplementary data S1 (table S1) for more details on the baseline characteristics.

Sequencing was performed in 45 of the 47 patients however it was not successful in 14 (31%) patients due to low viral loads. Sequencing was not performed in 2 due to a negative PCR test in one patient and a very low viral load in the other. Sequencing before and after treatment with sotrovimab was successful in 16 patients. Furthermore, 10 patients only had a sequencing result prior to sotrovimab treatment and 5 patients only had a sequencing result after sotrovimab treatment. Twenty-five patients were infected with the Omicron BA.1 subtype and 6 with the BA.2 subtype. Key Spike mutations were detected on positions 337 and 340 (known to confer in vitro resistance to sotrovimab) in 6/16 (38%) patients with successful sequencing before and after sotrovimab (Figure 1). These mutations were found in 4 of 25 (16%) BA.1 infected patients and in 2 of the 7 (29%) infected with BA.2. In a third BA.2 infected patient, a D796Y mutation was found but its impact on the neutralizing effect of sotrovimab is unknown. For more detailed information on the performance of sequencing and the characteristics of patients with Spike mutations, we refer to supplementary data S2 (table S2 and S3) and supplementary figure S1.

The median time to a Ct-value ≥30 was 15 days (IQR 8-22 days; range 3-149 days). In contrast, the median time to Ct-value ≥30 in patients with a Spike mutation was 50 days (IQR 14 – 67) days. In 5/7 (71%) patients with Spike mutations, low Ct-values persisted 37, 63, 64, 76 and 149 days after treatment with sotrovimab (Figure 1).

Discussion

Following treatment with sotrovimab, Spike mutations associated with reduced in vitro susceptibility were detected in 6 of 47 patients overall and in 6 of 16 in whom sequencing was successful after therapy.[9] Furthermore, 4 patients infected with BA.1 and one patient infected with BA.2 continued to have a high viral load more than 4 weeks after treatment with sotrovimab. In all 4 patients who were infected with BA.1 and had a prolonged infection, mutations were found at position 337 or 340.

Our observations show that prolonged viral replication can explained by treatment-related viral evolution towards resistance. This also illustrates that immunocompromised patients unable to clear SARS-CoV-2 despite antiviral therapy could serve as a source of new variants. These patients should be closely followed until viral clearance is documented whenever possible. Research is urgently needed to evaluate the value of direct acting antivirals in this patient group. Similar to the treatment of HIV, combination antiviral therapy might be required to reduce the risk for resistance. However, even when tixagevimab/cilgavimab combination therapy is used, only one of these antibodies retains in vitro activity against BA.2 and BA.4/5 variants. Therefore, monitoring treatment response with sequencing is recommended when available. An alternative treatment option may be very-high titer convalescent plasma that was harvested from donors with a history of Omicron infection who also are fully vaccinated and boostered, considering the polyclonal nature of convalescent plasma.[11, 12]

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Conflicts of interest

HS, OMB, GA and KM declare to have no personal conflicts of interest.

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Figure legends

Figure 1:

Title: Follow-up of viral load in immunocompromised patients infected with Omicron.

Abbreviations: Ct = cyclic threshold, RT-PCR = real time polymerase chain reaction.

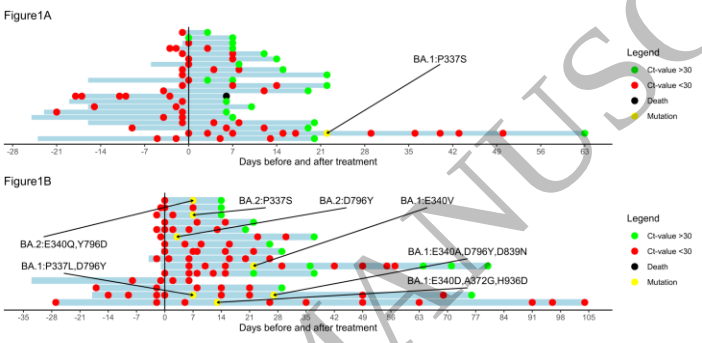

Figure 1
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