

Predictors of Coronavirus Disease 2019 Hospitalization After Sotrovimab in Patients With Hematologic Malignancy During the BA.1 Omicron Surge

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Background. Sotrovimab is an anti-spike neutralization monoclonal antibody developed to reduce the risk of coronavirus disease 2019 (COVID-19) progression and advancement to hospitalization in high-risk patients. Currently, there is limited research describing the association of sotrovimab treatment in patients with hematologic malignancy and the predictive factors of hospitalization.

Methods. We performed an observational study of 156 consecutive cancer patients who received sotrovimab at Memorial Sloan Kettering Cancer Center in New York City during the BA.1 Omicron surge. We evaluated the demographic, clinical, and laboratory characteristics of the patients who had subsequent COVID-19–related hospitalization(s) compared to those who did not.

Results. Among the 156 study patients, 17 (11%) were hospitalized, of whom 4 were readmitted for COVID-19–related complications; 3 deaths were attributed to COVID-19. Results from multivariable logistic regression show that significant factors associated with hospitalization include patients on anti-CD20 therapy (adjusted odds ratio [aOR], 5.59 [95% confidence interval {CI}, 1.73–18.12]; $P = .004$) and with relapse/refractory disease (aOR, 5.69 [95% CI, 1.69–19.16]; $P = .005$). Additionally, whole genome sequencing of severe acute respiratory syndrome coronavirus 2 detected high occurrences of mutations in the spike gene associated with treatment-related resistance longitudinal samples from 11 patients treated with sotrovimab.

Conclusions. While sotrovimab is effective at reducing COVID-19 hospitalization and disease severity in patients with hematologic malignancy when administered early, patients who received anti-CD20 antibodies showed substantial morbidity. Due to the high potential for resistance mutation to sotrovimab and increased morbidity in patients on anti-CD20 therapy, combination treatment should be explored to determine whether it provides added benefits compared to monotherapy.

Keywords. COVID-19; hematologic malignancy; monoclonal antibodies; SARS-CoV-2.

The use of monoclonal antibodies (mAbs) that retain activity against circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants has been the standard of treatment for patients at high risk for progression to severe coronavirus disease 2019 (COVID-19) [1]. The United States (US) Food and Drug Administration (FDA) has issued emergency use authorization (EUA) over the course of the COVID-19 pandemic of several mAbs for the treatment of mild to moderate COVID-19 in adult and pediatric patients aged ≥ 12 years. Among these, sotrovimab was given EUA designation in May 2021 based on a prespecified interim analysis

of a multicenter randomized controlled trial (RCT) that demonstrated an 85% risk reduction in disease progression in non-hospitalized patients with symptomatic COVID-19 before Omicron [2]. In addition, no patients treated with sotrovimab required oxygen support or mechanical ventilation [3]. Most patients in this trial did not have cancer but had other high-risk conditions including obesity, diabetes, and 2 or more medical conditions in 45% of the participants.

The Omicron variant that emerged in November 2021 encodes several amino acid substitutions in the spike protein, 15 of which are in the receptor-binding domain [4]. Because BA.1-specific mutations only had a marginal effect on sotrovimab binding [5, 6], this led to its preferential use during the BA.1 surge in the US. The FDA has since suspended sotrovimab EUA due to a reduction in neutralization against Omicron sublineages [7]. There is limited knowledge on the effectiveness of mAb treatment in specific patient groups. A critical gap in the pivotal trials arises from the minimal representation of high-risk cancer patients, such as those with hematologic malignancy (HM), who are among those at

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the highest risk for COVID-19 hospitalization and complications. Chronic infection that could perpetuate in host viral evolution due to antibody evasion is a primary concern in this population [8, 9]. Furthermore, the high-risk patient characteristics that predict hospitalization despite mAb treatment are unknown. Identifying predictors of COVID-19 progression after mAb treatment will help optimize treatment strategies for those at the highest risk for poor COVID-19 outcomes. The present study describes the predictors for hospitalization, clinical characteristics, and virologic outcomes in sotrovimab-treated patients with HM.

METHODS

Study Population

Memorial Sloan Kettering Cancer Center is a 574-bed tertiary cancer center in New York City with approximately 25 000 admissions and 173 000 patient-days annually.

From 21 December 2021 to 27 January 2022 during the BA.1 Omicron surge, all consecutive adult and pediatric patients with SARS-CoV-2 infection who received sotrovimab were included in the study. Patients who received sotrovimab on the day of hospital admission were excluded ($n = 8$). A retrospective analysis of 156 patients was conducted. All patients were followed up for at least 60 days after sotrovimab infusion until 30 April 2022. Identification of case patients and their medical background and clinical course during COVID-19 illness were extracted from electronic medical records. The Memorial Sloan Kettering Cancer Center Institutional Review Board granted a Health Insurance Portability and Accountability Act waiver of authorization to conduct this study.

Laboratory Methods

SARS-CoV-2 RNA Test

The viral RNA was detected in nasopharyngeal swabs or saliva samples as previously described [10]. In brief, real-time reverse-transcription polymerase chain reaction testing for SARS-CoV-2 RNA was performed using several commercial assays including the TaqPath COVID-19 Combo Kit (Thermo Fisher Scientific, Waltham, Massachusetts) targeting the N, S, and ORF genes; the Cobas SARS-CoV-2 test (Roche Molecular Diagnostics, Indianapolis, Indiana) targeting the ORF1 a/b and E genes; the BioFire Respiratory Panel 2.1 (bioMérieux, Salt Lake City, Utah); and the ePlex Respiratory Panel 2 (GenMark/Roche Molecular Diagnostics, Indianapolis, Indiana). Samples were reported as positive per the manufacturers' instructions. When available, the cycle threshold (Ct) value was retrieved from each instrument.

SARS-CoV-2 Whole Genome Sequencing

Whole genome sequencing (WGS) was performed on available samples with a Ct value < 30 to increase likelihood of successful

sequencing. Samples tested on platforms that do not provide Ct value (eg, BioFire RP 2.1 and ePlex 2) were WGS without knowledge of approximate viral loads. WGS was performed as previously described using the ARTIC protocol with version 4.1 primers (Integrated DNA Technologies, Coralville, Iowa) [11]. Pangolin software (<https://github.com/cov-lineages/pangolin>) was used to assign lineages for each consensus sequence using the Pango nomenclature for all sequences passing sequencing quality check. Mutation calling was performed by uploading all FASTA files to Nextclade version 2.2.0 (<https://clades.nextstrain.org>) [12].

Anti-SARS-CoV-2 spike immunoglobulin G antibody assay was performed as previously described [13].

Statistical Analysis

The 156 study patients were stratified into 2 groups based on COVID-19-related hospitalization. Clinical and demographic characteristics were examined for all patients. Univariate and multivariable logistic regression models were used to study risk factors for COVID-19-related hospitalizations. Initial univariate analysis was performed to screen the potential prognostic factors with a P value of $< .05$. The multivariable model was then developed by incorporating variables that were statistically significant in the univariate model. For variables with zero cell frequency, the Firth bias-correction method was used to address separation issues [14]. Multicollinearity was not a significant factor among the independent variables included in the multivariable model as the variance inflation factor (VIF) for each variable was < 2 (data not shown). Final selection of variables included in the multivariable model was done by applying a stepwise approach using logistic regression. Results from the models were expressed as odds ratio (OR) with 95% confidence interval (CI) and P value for statistical significance. Assumptions of model fit were assessed using the Hosmer-Lemeshow test, which confirmed the adjusted model was a good fit for the data ($P = .288$). The threshold for statistical significance was set at a 2-sided $P < .05$. All calculations were performed using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

Baseline Clinical Characteristics of the Study Cohort

During the study period, 156 high-risk patients with HM received sotrovimab. The median age was 61.5 years (range, 12–91 years) and 78 patients were male. The underlying cancers were lymphoma (62), leukemia and myelodysplastic syndrome (66), and myeloma/amyloidosis (28). Twenty-four patients had received hematopoietic stem cell transplant (HCT) or chimeric antigen receptor T-cell (CAR-T) therapy (10 autologous transplant, 11 allogeneic transplant, and 3 CAR-T recipients). The median time from cellular therapy to SARS-CoV-2 infection was 93.5 days (interquartile range, 54.5–127.8 days). Eighty-three patients had at least 1 additional

comorbid condition (Table 1). By the end of the study period, 152 were still alive.

Twenty-nine unique patients required all-cause hospital admission during the study follow-up period; 17 were hospitalized for COVID-19 management, and 4 patients contributed to 5 COVID-19–related readmissions (Table 2). The remaining hospitalizations were unrelated to COVID-19. Of the 156 study patients, 155 had no prior COVID-19 infection, and 2 patients received preexposure prophylaxis with Evusheld 5 and 8 days before COVID-19 diagnosis.

The median time to sotrovimab administration from symptom onset was 3 days (range, 0–16 days), and from laboratory diagnosis, 0–9 days. One hundred twenty six patients with available records were fully vaccinated. Study patients were considered fully vaccinated for COVID-19 ≥ 2 weeks after the final dose of a primary vaccination series. Serological assessment (anti-SARS-CoV-2 spike antibody levels, Abbott) before and after COVID-19 diagnosis and sotrovimab treatment were available for 89 COVID-19–vaccinated patients (Supplementary Figure 1).

Comparison Between Hospitalized Versus Nonhospitalized Sotrovimab Recipients

As shown in Table 1, notable findings on univariable analysis showed higher odds of hospitalization among those with refractory or relapsed cancer (OR, 3.52 [95% CI, 1.25–9.96]; $P = .017$) and patients who received anti-CD20 therapy within the previous 12 months (OR, 4.27 [95% CI, 1.51–12.03]; $P = .006$). Patients with atrial fibrillation ($P = .007$) and heart failure ($P = .009$) were also significant in univariable analysis. Multivariable logistic regression adjusting for significant factors associated with hospitalization on univariable analysis demonstrated that the ORs for anti-CD20 therapy (adjusted OR [aOR], 5.59 [95% CI, 1.73–18.12]; $P = .004$) and relapse/refractory disease (aOR, 5.69 [95% CI, 1.69–19.16]; $P = .005$) increased, with significant associations maintained. Atrial fibrillation and heart failure were not significant after covariate adjustment. Among the laboratory findings, neutropenia and lymphopenia (absolute lymphocyte count < 500 cells/ μL) prior to COVID-19 diagnosis were not significant predictors of hospitalization. Other notable factors that did not predict hospitalization included age; time to sotrovimab administration from symptom onset; vaccination status; comorbidities; underlying cancer type; previous cellular therapy; or HCT, systemic chemotherapy, or steroids within 30 days prior to COVID-19 diagnosis. The median time to hospitalization from symptom onset and sotrovimab administration was 17.0 and 3.0 days, respectively (Supplementary Figure 2). Symptom onset dates were not available for 13 patients.

Clinical Outcome of Hospitalized Patients, Duration of Viral Shedding, and SARS-CoV-2 Viral Evolution

The clinical presentation and outcomes of the 17 patients during their index hospitalization are summarized in Table 2.

Fever and dyspnea were the most common presenting symptoms at hospitalization, 6 patients required oxygen support, and 15 had radiographic evidence of lower airway involvement. Most patients received standard of care therapy with remdesivir and dexamethasone. The illness severity was mild to moderate for 15 of the 17 patients. One patient was intubated and died after 2 days of ventilatory support. Overall, 3 deaths were attributed to COVID-19 where 1 occurred at index admission and 2 upon readmission.

Four of the 17 hospitalized patients were readmitted for COVID-19–related issues with 1 patient readmitted twice. The COVID-19 severity for these 5 readmissions was either moderate (3/5 [60%]) or severe/critical (2/5 [40%]). All had received anti-CD20 therapy within the preceding year. One unvaccinated patient with mantle cell lymphoma with rituximab-based therapy (last dose 4 months prior) had 3 admissions characterized by fevers and worsening shortness of breath despite antibiotics and 2 courses of steroids and remdesivir. Additionally, the patient also received treatment with baricitinib. Despite this, the patient remained oxygen-dependent for 3 months. Of the 3 other readmitted patients, 1 developed chronic COVID-19 infection and 2 died from progressive respiratory failure attributed to COVID-19. Chronic COVID-19 infection is defined as patients who have had progressive or recurrent COVID-19–related symptoms (or require home oxygen) with imaging consistent with COVID-19 and, in the absence of an alternate etiology, with or without evidence of viral persistence.

Time from viral detection to viral clearance for the 156 study patients before and after sotrovimab showed 62 patients with negative results by the end of the study period with a median time to viral clearance at 62.5 days (range, 8–133 days) (Supplementary Figure 3). Only patients with 3 or more samples were included for longitudinal mutational analysis. Overall, 80 samples were available for WGS from 13 patients, including 57 specimens from 8 hospitalized patients and 23 samples from 5 nonhospitalized patients. Samples before and after sotrovimab were available for 12 of the 13 patients. The following Omicron subvariants were identified among these: BA.1, BA.1.1, BA.1.1.10, BA.1.15, and BA.1.17.2. The mutational analysis for the available samples is shown in Figure 1 by hospitalization status. WGS detected mutations in the spike gene associated with resistance to sotrovimab (P337R/S, E340A/K/D, K356T) in 11 patients; 8 of 8 hospitalized patients with available samples developed treatment-related mutations. Additionally, 3 nonhospitalized patients also showed evidence of treatment-related mutations. Mutations were first detected in samples collected between 8 and 43 days following initiation of treatment with sotrovimab (median, 20 days); 10 of 11 patients showed no evidence of mutations before day 8 from receipt of sotrovimab. One patient did not have available sequencing results until day 34 following sotrovimab when

Table 1. Univariable and Multivariable Logistic Regression Analyses of Risk Factors for Coronavirus Disease 2019–Related Hospitalizations in 156 High-Risk Patients With Hematologic Malignancy Who Received Early Treatment With Sotrovimab^a

Characteristic	Admits Cases (No Admits) (n = 156)	Univariate Model ^b		Multivariable Model ^b	
		OR (95% CI)	P Value*	OR (95% CI)	P Value*
Age ≥65 y	7 (60)	.92 (.33–2.56)	.876	...	
Age <65 y	10 (79)	1.00		...	
Female sex	8 (70)	.87 (.32–2.40)	.797	...	
Male sex	9 (69)	1.00		...	
Days to sotrovimab from symptom onset ^c					
>10 d	2 (4)	4.68 (.77–28.54)	.094	...	
6–10 d	3 (20)	1.41 (.36–5.49)	.625	...	
0–5 d	11 (103)	1.00	NA	...	
Creatinine ≥1.1 mg/dL ^d	3 (38)	.56 (.15–2.05)	.380	...	
Creatinine <1.1 mg/dL ^d	14 (99)	1.00		...	
Lymphocyte count ≥500 cell/μL ^e	13 (116)	.616 (.18–2.07)	.433	...	
Lymphocyte count <500 cell/μL ^e	4 (22)	1.00		...	
CD3 ⁺ CD4 ⁺ (T4 helper) cells, blood ≥200 cell/μL ^f	4 (27)	.37 (.09–1.52)	.169	...	
CD3 ⁺ CD4 ⁺ (T4 helper) cells, blood <200 cells/μL ^f	6 (15)	1.00		...	
CD19 ≥50 cells/μL ^f	2 (16)	.39 (.07–2.15)	.281	...	
CD19 <50 cells/μL ^f	7 (22)	1.00		...	
Neutrophils ≥0.5 k/μL ^g	16 (118)	.54 (.06–5.16)	.595	...	
Neutrophils <0.5 k/μL ^g	1 (4)	1.00		...	
Total IgG ≥500 mg/dL	8 (64)	0.94 (0.26–3.36)	.921	...	
Total IgG <500 mg/dL	4 (30)	1.00		...	
Anti-spike SARS-CoV-2 antibody level (Abbott) ^h					
≥500 AU/mL	3 (22)	1.14 (.26–4.96)	.865	...	
<500 AU/mL	6 (50)	1.00		...	
COVID-19 vaccination status ⁱ					
Fully vaccinated	14 (112)	1.13 (.30–4.19)	.861	...	
Not fully vaccinated	3 (27)	1.00		...	
Comorbidities ^j					
At least 1 comorbidity	11 (72)	1.71 (.60–4.87)	.318	...	
No comorbidity	6 (67)	1.00		...	
Atrial fibrillation (yes)	5 (10)	5.38 (1.58–18.31)	.007*	3.68 (.77–17.54)	.102
Atrial fibrillation (no)	12 (129)	1.00		1.00	
COPD (yes)	2 (7)	2.52 (.48–13.22)	.276	...	
COPD (no)	15 (132)	1.00		...	
Heart failure (yes)	3 (3)	9.71 (1.79–52.76)	.009*	6.89 (.85–56.11)	.071
Heart failure (no)	14 (136)	1.00		1.00	
HIV positive	0 (2)	1.57 (.04–67.0)	.814	...	
HIV negative	17 (137)	1.00		...	
Diabetes (yes)	4 (22)	1.64 (.49–5.49)	.425	...	
Diabetes (no)	13 (117)	1.00		...	
Hypertension (yes)	7 (49)	1.29 (.46–3.59)	.631	...	
Hypertension (no)	10 (90)	1.00		...	
Renal failure (yes)	4 (23)	1.55 (.46–5.18)	.475	...	
Renal failure (no)	13 (116)	1.00		...	
Systemic steroids (yes) ^k	8 (57)	1.28 (.47–3.51)	.631	...	
Systemic steroids (no) ^k	9 (82)	1.00		...	
Anti-CD20 therapy (yes) ^l	9 (29)	4.27 (1.51–12.03)	.006*	5.59 (1.73–18.12)	.004*
Anti-CD20 therapy (no) ^l	8 (110)	1.00		1.00	
Cancer type					
Leukemia/MDS	5 (61)	.48 (.15–1.53)	.216	...	
Myeloma/amyloidosis	3 (25)	.71 (.18–2.84)	.625	...	
Lymphoma	9 (53)	1.00	NA	...	
Chemotherapy (yes) ^m	12 (82)	1.67 (.56–5.00)	.36	...	
Chemotherapy (no) ^m	5 (57)	1.00		...	
Relapse/refractory disease (yes)	8 (28)	3.52 (1.25–9.96)	.017*	5.69 (1.69–19.16)	.005*

Table 1. Continued

Characteristic	Admits Cases (No Admits) (n = 156)	Univariate Model ^b		Multivariable Model ^b	
		OR (95% CI)	P Value*	OR (95% CI)	P Value*
Relapse/refractory disease (no)	9 (111)	1.00		1.00	
BMT CAR-T (yes) ⁿ	2 (22)	.71 (.15–3.34)	.663	...	
BMT CAR-T (no) ⁿ	15 (117)	1.00		...	
BMI, kg/m ^{2o}					
Underweight (<18.5)	0 (4)	.71 (.02–20.6)	.842	...	
Normal weight (18.5–24.9)	6 (41)	1.00	NA	...	
Overweight (25.0–29.9)	8 (46)	1.17 (.38–3.56)	.786	...	
Obese (≥30.0)	1 (40)	.24 (.04–1.50)	.126	...	

Abbreviations: Ab, antibody; BMI, body mass index; BMT, bone marrow transplant; CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; IgG, immunoglobulin G; MDS, myelodysplastic syndrome; NA, not applicable; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

^aData include 2 patients who received pre-exposure prophylaxis with Evusheld prior to COVID-19 diagnosis.

^bORs and P values calculated from logistic regression applying Firth correction, where appropriate.

^cSymptom onset is COVID-19 related. Onset date not available for 13 patients. Symptom onset to sotrovimab administration ranged from 0 to 16 days (median, 3 days).

^dCreatinine and IgG: Most recent values before COVID-19 diagnosis within the last 6 months.

^eLymphocytes: Most recent 3 laboratory values within 12 months prior to COVID-19 diagnosis. All 3 counts must be <500 cells/μL to be in the “<500” category. At least 1 count of value ≥500 cells/μL is considered in the “≥500” category. One patient did not have 3 laboratory values prior to COVID-19 diagnosis.

^fCD4 and CD19: Most recent values before COVID-19 diagnosis within the last year.

^gNeutrophils: Most recent values before COVID-19 diagnosis within the last month.

^hAnti-spike antibody: Most recent test value before COVID-19 diagnosis within 1 year. Excludes 2 patients who received Evusheld prior to sotrovimab.

ⁱStudy patients were considered fully vaccinated for COVID-19 ≥2 weeks after the final dose of a primary vaccination series. Not fully vaccinated: No vaccination records were available for these patients.

^jComorbidities (atrial fibrillation, COPD, heart failure, HIV, hypertension, diabetes, renal failure) are based on *International Classification of Diseases, Tenth Revision* diagnosis codes within 12 months of study period.

^kSystemic steroids include patients who were on steroids within 30 days prior to COVID-19 diagnosis. Includes dexamethasone, methylprednisolone, hydrocortisone, and prednisone.

^lAnti-CD20 therapy within previous 12 months from receipt of sotrovimab. This includes rituximab, obinutuzumab, tafasitamab, hyaluronidase-rituximab, and ofatumumab.

^mChemotherapy during study period.

ⁿBMT and CAR-T therapy combined. Service dates are prior to COVID-19 diagnosis and sotrovimab treatment and are within 1 year of study period.

^oMost recent value during past 12 months; 10 patients did not have BMI values.

*Statistical significance at α = .05.

E340D was detectable. The maximum duration of detection of a viral escape variant was 90 days following sotrovimab.

DISCUSSION

In our study cohort of highly vaccinated high-risk hematologic malignancy patients during the Omicron BA.1 surge, 11% of sotrovimab recipients were hospitalized for COVID-19 management, 1.2% required intensive care unit (ICU) level of care, and 3 patients died due to COVID-19. Refractory or relapsed malignancy and anti-CD20 therapy were significant predictors of hospitalization, but recent chemotherapy and steroid treatment did not influence this risk. Longitudinal evaluation of respiratory samples from hospitalized patients showed a high frequency of sotrovimab-related mutations that emerged within 8 to 43 days of treatment.

Early treatment with mAb reduces the risk of hospitalization and other COVID-19-related complications. In a pivotal international RCT, 1% of the sotrovimab-treated patients required hospitalization by day 29 compared to 7% in the placebo group [2]. The postauthorization experience among immunocompromised patients has most commonly been reported in solid

organ transplant (SOT) recipients, with hospitalization rates ranging from 3% to 16% [15, 16]. Solera et al found a 30-day COVID-19-related hospitalization rate of 16% in SOT recipients who received sotrovimab; 4.7% required oxygen with no COVID-19-related ICU admissions, and no patients required mechanical ventilation [17]. Compared to these reports, our COVID-19-related hospitalization risk in patients with HM is 11% (17 of 156), with most (n = 15) hospitalized patients having mild to moderate manifestations.

Experience with sotrovimab in high-risk patients with HM, especially patients who have received anti-CD20 therapies, has not been extensively reported. Before the availability of vaccines and COVID-19 treatments, HM was consistently associated with higher hospitalization rates and complications in multiple reports [18, 19]. Moreover, although the risk of adverse outcomes is mitigated in the post-vaccine era, COVID-19-related complications remain common among patients undergoing treatment for HM [20, 21]. For example, in the study by Mittelman et al, the relative risk of hospitalization and severe disease was 3.13 and 2.27, respectively, in vaccinated patients with HM compared to matched controls without HM [21]. The overall risk was highest for those on active treatment.

Table 2. Clinical Characteristics and Outcomes During Index Hospitalization for 17 Patients Hospitalized After Receiving Sotrovimab

Characteristic	No. (%) ^a
Age, y, median	63
Sex, female	9 (52.9)
Unvaccinated	2 (11.8)
Symptoms at hospitalization	
Fever	13 (76.5)
Dyspnea	9 (52.9)
Cough	11 (64.7)
Nasal congestion	2 (11.8)
Poor oral intake	7 (41.2)
Chest pain	3 (17.6)
Fatigue	5 (29.4)
CT chest findings (n = 9)	
Bilateral consolidative opacities	2 (22.2)
Bilateral patchy ground-glass opacities	8 (89.0)
CXR findings (n = 8)	
Unilateral opacities	3 (37.5)
Bilateral opacities	3 (37.5)
Clear lungs	2 (25)
Oxygen requirement	
No oxygen requirement or <24 h	11 (64.7)
Nasal cannula (>24 h)	4 (23.5)
High-flow oxygen	1 (5.9)
Mechanical ventilation	1 (5.9)
COVID-19 severity ^b	
Mild	11 (64.7)
Moderate	4 (23.5)
Severe/critical	2 (11.8)
COVID-19 treatment	
Any COVID-19 treatment	14 (82.4)
Remdesivir	13 (76.5)
Dexamethasone	6 (35.3)
ICU-level care for COVID-19	1 (5.9)
Outcomes	
COVID-19–related death ^c	3 (17.6)
COVID-19–related readmission	4 (23.5)
Chronic infection ^d	3 (17.6)
Length of stay, d, median (range)	8 (1–64)

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; CXR, chest radiograph; ICU, intensive care unit.

^aPatients can be in >1 category.

^bCOVID-19 severity based on maximum oxygen requirement through admission. Mild infections remained on room air or required nasal cannula <24 hours; moderate infections required nasal cannula >24 hours; severe/critical infections required high-flow oxygen or intubation.

^cCOVID-19–related deaths are based on review of electronic medical records and clinical judgment of patient presentation/illness in relation to the patients' primary disease and time from COVID-19 positivity.

^dChronic COVID-19 infection is defined as patients who have had progressive or recurrent COVID-19–related symptoms (or require home oxygen) with imaging consistent with COVID-19 and, in the absence of an alternate etiology, with or without evidence of viral persistence.

Low CD8⁺ T-cell responses during acute infection predict severe disease, and B-cell depletion in hematologic cancers has been linked with chronic persistent COVID-19 [9]. Early mAb treatment can overcome some of these viral-specific immune deficits and improve patient outcomes. In our cohort, anti-CD20 therapy was a significant predictor of

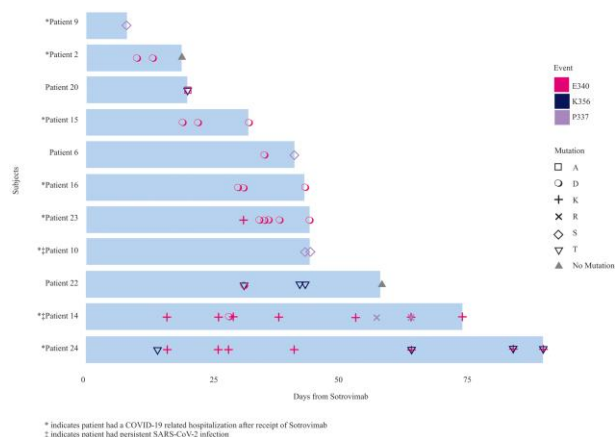


Figure 1. Various spike protein mutations associated with resistance identified following receipt of sotrovimab in 11 patients, including 8 hospitalized cases and 2 persistent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. *Patient had a coronavirus disease 2019–related hospitalization after receipt of sotrovimab. #Patient had a persistent SARS-CoV-2 infection.

hospitalization: 38 patients received anti-CD20 therapies in our study cohort within the preceding 12 months of sotrovimab treatment (median, 5 months). Among these, 30 were fully vaccinated against COVID-19, 9 required hospitalization, 3 were readmitted (with 1 patient readmitted twice), and 3 died due to COVID-19 complications. Two of the 38 anti-CD20 recipients had evidence of persistent infection. Despite the early use of sotrovimab, there remains substantial morbidity in this population. Additional assessment of therapeutic approaches, including combination treatments, is warranted.

While there is an advantage in reducing hospitalization with the rapid administration of mAb, attention to the emergence of resistant viral escape variants is paramount, especially among immunocompromised hosts. Our data corroborate the phenomenon reported in Rockett et al and Destras et al in that sotrovimab use in immunocompromised patient populations may promote the rapid emergence of escape mutations [8, 22]. A recent analysis of 16 sotrovimab-treated patients, mostly SOT recipients and some on B-cell–depleting therapies, showed evidence of mutations in 6 of the 16 analyzed patients, although not all had serial samples available to follow the emergence of mutations [23]. Whether patients with HM harbor treatment resistance mutations to a higher degree than other high-risk groups and the public health implications of these findings are unclear at this time.

There are several limitations to our study. The most important limitation is the small sample size and a small number of COVID-19–related hospitalizations, which did not allow for a robust multivariable analysis. Of note, the heterogeneity of the transplant or CAR-T recipients and its small sample size with only 2 hospitalizations preclude additional analyses to identify predictors within this group. As a result, we could

have missed detecting other predictors of disease progression. Additionally, our report includes the most extensive cohort experience from a homogenous high-risk hematologic malignancy group. We did not have a contemporary group of non-mAb-treated hematologic malignancy patients, so we were therefore unable to measure the effectiveness of mAb treatment in this population; however, this was not the primary goal of our study. Furthermore, relevant immune parameters such as CD19⁺ B cells and CD4 lymphocyte counts were not entirely available for analysis, nor can we confirm whether patients without vaccination records were immunized elsewhere. In addition, we did not perform viral sampling and serological assessments at predetermined intervals. Nonetheless, there was still a substantial number of analyzable samples to draw meaningful conclusions. Last, because our cohort had a high rate of COVID-19 vaccination (>80%), findings cannot be extrapolated to unvaccinated high-risk patients with HM.

In summary, early sotrovimab use reduced COVID-19–related hospitalization and severity in high-risk hematologic malignancy patients. However, there is a high occurrence of treatment-related mutations. Most importantly, patients treated with anti-CD20 therapies remain at higher risk for COVID-19–related adverse outcomes. Due to the high potential for resistance mutation to sotrovimab and increased morbidity in patients on anti-CD20 therapy, combination treatment should be explored to determine whether it provides added benefits compared to monotherapy.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. Y. and M. K. were responsible for the conception and design of the study, interpretation of the data, and preparation of the manuscript. M. K. managed the study. J. Y., S. N. S., J. F., C. T., J. L. N. C., and S. K. S. acquired the data. J. Y., E. V. R., N. E. B., and R. K. analyzed the data. J. Y. performed statistical analysis. J. Y., E. V. R., and R. K. produced the figures and tables. T. M., N. E. B., and K. J. analyzed laboratory samples. All authors reviewed the final draft, critically reviewed and contributed to the writing of the manuscript, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Data availability. All sequences were uploaded to GISAID. For original data, please contact yanj7@mskcc.org.

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