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TRANSPLANT INFECTIOUS DISEASE

LETTER TO THE EDITOR

Comparative outcomes after early Sotrovimab administration in vaccinated and unvaccinated kidney transplant recipients with SARS-CoV-2 infection during the Delta and Omicron BA.1 surges

Organ transplant recipients respond suboptimally to SARS-CoV-2 vaccination and remain at risk for severe COVID-19 infections. During community surges with the Delta (September to November 2021) and Omicron BA.1 (December 2021 to February 2022) variants in Singapore, we systematically offered Sotrovimab to kidney transplant recipients (KTRs) who reported a positive antigen rapid test with diagnosis subsequently confirmed by SARS-CoV-2 PCR. Inclusion criteria were presentation within 6 days of symptom onset, were unvaccinated, or vaccinated with spike antibody <100 U/ml, (SpAb, Roche Cobas SARS-CoV-2-S assay) and not requiring oxygen.

We herein report outcomes among 51 SARS-CoV-2-infected KTRs administered 500 mg intravenous Sotrovimab. Note that 80.4% of the study population had received two or three doses of SARS-CoV-2 mRNA vaccine (Table 1A). Antimetabolite doses were halved upon COVID-19 diagnosis and discontinued with progression; calcineurin inhibitors and mTOR inhibitors were reduced or discontinued with progression and COVID-19 therapeutics administered as per NIH guidelines.[1] The association of independent variables with the outcomes of acute kidney injury (AKI), requirement for supplemental oxygen (SuppO2), intensive care unit (ICU), and mortality at 60 days follow-up were evaluated.

Overall, 15 (29.4%) had AKI, 11 (21.6%) required SuppO2, nine (17.6%) required ICU, and five (9.8%) died. On multivariable analysis, baseline estimated estimated glomerular filtration rate (eGFR) ≤30 ml/min/1.73m^2 was the only variable significantly associated with AKI and mortality (Table 1B). BMI, lung infiltrates on admission, and interval to Sotrovimab ≥4 days were independently associated with SuppO2 requirement, while BMI, eGFR, and lung infiltrates were independently associated with ICU stay.

Our retrospective study, although limited by small numbers, demonstrates that despite Sotrovimab, 21.6% of KTRs progressed to severe disease, in contrast to only 1% progression in the COMET-ICE trial, which included unvaccinated, nonimmunosuppressed individuals.[2] Nevertheless, early Sotrovimab modified disease progression: 14.3% of KTRs administered Sotrovimab at <4 days after symptom onset needed SuppO2 versus 55.6% among those treated at ≥4 days (p = .015). Virus- and host-related factors contributed significantly to progression: lung infiltrates occurring at 2 days after symptom onset implied rapid disease progression in an immunocompromised host and portended a high risk for SuppO2 and ICU. Surprisingly, there were no differences in outcomes between nonimmune Sotrovimab-treated KTRs infected during the Delta versus Omicron BA.1 surges, despite Omicron's purported mildness.[3] Omicron's known immune evasive properties, and suboptimal underlying immunity of KTRs, as apparent from SpAb <100 U/ml among 55.6% of our vaccinated patients, may both be factors.[4]

Our approach to administer Sotrovimab only to unvaccinated and vaccine-nonresponders allowed risk stratification and may be adopted in future studies on COVID-19 therapeutics. Alternatively, administering Sotrovimab to those with comorbidities, as utilized by Chavarot et al., is reasonable, given the association of adverse outcomes with low eGFR and high BMI.[5]

In summary, although 21.6% of KTRs progressed to severe COVID-19 infection despite Sotrovimab during our Delta and BA.1 Omicron surges, treatment within 4 days of symptom onset mitigated disease severity. More effective vaccine and therapeutic strategies are needed for vulnerable populations, especially given the SARS-CoV-2 virus's ability to evolve and escape both natural and vaccine-induced immunity and current immune therapeutics.

AUTHOR CONTRIBUTIONS

Concept and design: Anantharaman Vathsala, Jyoti Somani, Matthew Ross D'Costa, Lionel Lum, Emmett Tsz-Yeung Wong, and Hersharan Kaur Sran. *Acquisition, analysis, or interpretation of data*: Anantharaman Vathsala, Jyoti Somani, Matthew Ross D'Costa, Lionel Lum, Emmett Tsz-Yeung Wong, and Hersharan Kaur Sran. *Drafting of the manuscript*: Vathsala and Somani. *Critical revision of the manuscript for important intellectual content*: Anantharaman Vathsala, Jyoti Somani, Matthew Ross D'Costa, Lionel Lum, Emmett Tsz-Yeung Wong, and Hersharan Kaur Sran. *Statistical analysis*: Vathsala and Somani. Drs Vathsala and Somani had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Abbreviations: 95% CI, 95% confidence interval; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; KTR, kidney transplant recipients; OR, odds ratio; SpAb, spike antibody; SuppO2, supplemental oxygen.

TABLE 1 Descriptive statistics and outcomes (Table 1A) and multivariable regression analysis (Table 1B) on outcomes for kidney transplant recipients with COVID-19 infection treated with Sotrovimab

Table 1A: *Demographics, clinical characteristics, infection-related parameters, and outcomes for study population, stratified by period of infection*[a]

		Period of infection[c]	
	Study population administered Sotrovimab[b]	Period 1: September–November 2021	Period 2: December 2021–February 2022
Demographics			
Number	51	25 (49%)	26 (51%)
Male gender	27 (52.9%)	18/25 (72%)	9/26 (34.6%)
Ethnicity			
- Chinese	31 (60.8%)	16/25 (64%)	15/26 (57.7%)
- Malay	13 (25.5%)	6/25 (24%)	7/26 (26.9%)
- Indian	6 (11.8%)	3/25 (12%)	3/26(11.5%)
- Others	1 (2%)	0/25 (0%)	1/26 (3.8%)
Age, years	55.2 (12.1)	57.7 (10.7)	52.7 (13)
- ≥65 years	10 (19.6%)	7 (28%)	3 (11.5%)
Deceased donor transplant	33 (64.7%)	19/25 (76%)	14/26 (53.8%)
Characteristics at time of admission with COVID-19			
Interval posttransplant, years	10.1 (7.2)	11.5 (7.5)	8.8 (6.8)
Diabetes	26 (51%)	16/25 (64%)	10/26 (38.5%)
Body mass index, kg/m^2 (BMI, median, IQR)	24.2 (6.1)	24.8 (4.5)	23.9 (7.0)
- BMI >30	6 (11.8%)	4/25 (16%)	2/26 (7.7%)
Baseline serum creatinine, μmol/L (median, IQR)	118 (64)	118 (62)	122 (88)
Baseline estimated glomerular filtration rate (eGFR),[d] ml/min/1.73 m^2	53.7 (23.4)	57.3 (22.2)	50.2 (24.5)
- eGFR ≤ 30 ml/min/1.73 m^2	9 (17.6%)	3 (12%)	6 (23.1%)
Charlson co-morbidity score[e]	2.7 (2.1)	3.0 (2.4)	2.5 (1.8)
- ≥5	10 (19.6%)	7/25 (28%)	3/26 (11.5%)
Immunosuppression:			
- Tacrolimus-mycophenolate-prednisolone	22 (43.1%)	14/25 (56%)	8/26 (30.8%)
- Cyclosporine-mycophenolate-prednisolone	20 (39.2%)	7/25 (28%)	13/26 (50%)
- Other regimens	9 (17.6%)	4/25 (16%)	5/26 (19.2%)
Vaccination status at infection:			
- Nil vaccination	5 (9.8%)	4/25 (16%)	1/26 (3.8%)
- 1 dose or ≤14 days after 2nd Dose	5 (9.8%)	5/25 (20%)	0/26 (0%)
- >14 days after 2nd dose and ≤14 days after 3rd dose	19 (37.3%)	15/25 (60%)	4/26 (15.4%)
- >14 days after 3rd dose	22 (43.1%)	1/25 (4%)	21/26 (80.8%)
Type of 1st and 2nd dose vaccination among those receiving at least 2 doses			
- Number of KTR >14 days after 2nd dose of SARS-CoV-2 vaccination	41	16	25
- BNT162b2, Pfizer-BioNTech	40 (97.6%)	15/16 (93.8%)	25/25 (100%)
- mRNA-1273, Moderna	1 (2.4%)	1/16 (6.3%)	0/25 (0%)
- Sinovac	-	-	

(Continues)

TABLE 1 (Continued)

Table 1A: *Demographics, clinical characteristics, infection-related parameters, and outcomes for study population, stratified by period of infection*[a]

		Period of infection[c]	
	Study population administered Sotrovimab[b]	Period 1: September–November 2021	Period 2: December 2021–February 2022
COVID-19-related parameters			
Interval from symptom onset to admission, days	2.3 (1.2)	2.5 (1.4)	2.0 (1.0)
Symptoms and signs of COVID-19 infection at admission			
- Fever, without respiratory tract symptoms, other, or no symptoms	6 (11.8%)	4/25 (16%)	2/26 (7.7%)
- Upper respiratory tract symptoms	36 (70.6%)	14/25 (56%)	22/26 (84.6%)
- Lung infiltrates on chest radiograph	9 (17.6%)	7/25 (28%)	2/26 (7.7%)
Spike antibody			
- Not vaccinated or nonreactive	32 (62.7%)	21/25 (84%)	11/26 (42.3%)
- 0–100 U/ml	19 (37.3%)	4/29 (16%)	15/26 (57.7%)
- >100 U/ml	-	-	-
Cycle threshold, (median, IQR)	16.6 (3.1)	16 (2.8)	17.2 (3.0)
ISARIC-4C score at admission[f]	5.2 (3.0)	6.0 (3.1)	4.5 (2.9)
- Score ≥ 9	8 (15.7%)	6/21 (24%)	2/26 (7.7%)
Interval to Sotrovimab from symptom onset, days	2.3 (1.2)	2.5 (1.4)	2.0 (1.0)
- ≥4 Days	9 (17.6%)	7/25 (28%)	2/26 (7.7%)
Additional therapies for COVID-19 infection[g]			
- Nil	42 (82.4%)	19/25 (76%)	23/26 (88.5%)
- Dexamethasone	9 (17.6%)	6/25 (24%)	3/26 (11.5%)
- Remdesivir	9 (17.6%)	6/25 (24%)	3/26 (11.5%)
- Baricitinib	6 (11.8%)	4/25 (16%)	2/26 (7.7%)
- Tocilizumab	2 (3.9%)	1/25 (4%)	1/26 (3.8%)
Outcomes[h]			
Acute kidney injury[i]	15 (29.4%)	6/25 (24%)	9/26 (34.6%)
Required supplemental oxygen	11 (21.6%)	8/25 (32%)	3/26 (11.5%)
Required intensive care stay	9 (17.6%)	6/25 (24%)	3/26 (11.5%)
Mortality	5 (9.8%)	4/25 (16%)	1/26 (3.8%)

CONFLICT OF INTEREST

The authors of this manuscript have no conflict of interest to disclose as described by the *American Journal of Transplantation*.

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ETHICS STATEMENT

This study was approved by the NHG Domain Specific Review Board (approval number: 2021/01164).

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TABLE 1 Continued

Table 1B: *Multivariable regression analysis of association of clinical characteristics and infection-related parameters on outcomes after COVID-19 infection*[j]

	Acute kidney injury[i]			Required supplemental oxygen			Required ICU stay			Mortality		
Dependent variable	**OR[k]**	**95% CI**	***p*-Value**	**OR[k]**	**(95% CI)**	***p*-Value**	**OR[k]**	**(95% CI)**	***p*-Value**	**OR[k]**	**(95% CI)**	***p*-Value**
Age ≥ 65 Years	-	-	-	6.81	(.48–95.81)	.155	-	-	-	6.99	(.44–112.23)	.17
Body mass index >30 kg/m^2	6.11	(.80–46.67)	.081	**48.89**	**(2.47–967.88)**	**.011**	**19.80**	**(1.03–380.44)**	**.048**	-	-	-
Baseline estimated glomerular filtration rate (eGFR) ≤30 ml/min/1.73 m^2	**14.79**	**(2.43–90.15)**	**.003**	-	-	-	**18.53**	**(1.28–268.59)**	**.032**	**32.52**	**(1.98–532.84)**	**.015**
Lung infiltrates on chest radiograph at admission	-	-	-	**36.24**	**(2.40–547.92)**	**.010**	**82.48**	**(4.57–1489.39)**	**.003**	7.71	(.48–124.79)	.15
Interval to Sotrovimab from symptom onset, ≥4 Days	-	-	-	**26.79**	**(1.74–411.96)**	**.018**	-	-	-	-	-	-

[a]All data in Table 1A are means and standard deviations (SD) as for normally distributed parameters unless otherwise specified; medians and interquartile range (IQR) are indicated for parameters not normally distributed. Numbers and proportions (%) are shown. Demographics, characteristics at time of COVID-19 infection, COVID-19-related parameters, and outcomes, stratified by period of infection, are shown.

[b]Of 102 presenting to our hospital with SARS-CoV-2 infection, 45 KTR were not treated with Sotrovimab due to spike antibody levels >100 U/ml in 34, presentation at greater than 5th day of illness in 6, requirement for oxygen therapy at presentation in 2, patient refusal in 3. In addition, 6 KTR received Sotrovimab prior to result availability and had Spike Antibody levels >100 U/ml. These patients were hence excluded from the Sotrovimab study population.

[c]The study population was stratified by period of infection. SARS-CoV-2 viral strains during these two periods of community surges in Singapore were predominately Delta between July 2021 to mid-December 2021 with the Omicron BA.1 surge beginning in mid-December 2021, waning from March 2022 onwards. There was a lower proportion of males ($p = .007$), a higher proportion of those having received SARS-CoV-2 vaccination ($p < .001$), and hence a higher proportion with reactive spike antibody levels 0–100 U/ml ($p = .003$) and higher cycle threshold values ($p < .008$) among patients infected during Period 2. There were no other differences for the other parameters between the two periods.

[d]eGFR calculated by the chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

[e]For calculation of the Charlson comorbidity score, chronic kidney disease was attributed a score of zero if eGFR was >45 ml/min/1.73 m^2.

[f]The ISARIC-4C mortality score is a risk stratification tool that has been developed to predict mortality for hospitalized COVID-19 patients. The score includes eight variables derived from initial hospital evaluation, including age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness, urea level (Blood Urea Nitrogen, mg/dL), and C reactive protein, for a total score of 0–21 points.

[g]KTR with disease progression were treated with therapeutic agents as per National Institute of Health recommendations as shown. As KTR with severe COVID-19 infection received more than one additional therapeutic agent, the percentages will not add up to 100%. There was no significant difference in proportions requiring additional therapies in the two periods.

[h]Outcomes were compared for the Sotrovimab-treated study population in the two periods, by Pearson chi-square analysis. There was no association of period of infection with any of the outcomes.

[i]Acute kidney injury was defined by increase in serum creatinine by at least ≥26.5 μmol/L or increase by ≥150 to 200% of baseline values.

[j]Binary Logistic multivariable regression analysis (Table 1B) was performed to determine the association of independent variables on the outcomes of acute kidney injury (AKI), requirement for supplemental oxygen (SuppO2), ICU stay (ICU), and Mortality. Independent variables were included in the multivariable analysis if deemed clinically significant (age, diabetes, BMI, baseline eGFR, interval posttransplant, presence of spike antibody, presence of lung infiltrates on admission chest radiograph) or if demonstrating significance with a *p*-value <.05 on univariate analysis. On univariate analysis, baseline eGFR ≤30 ml/min/1.73 m^2 was associated with all adverse outcomes- (odds ratio [OR] and 95% confidence interval [95% CI]: 14.88 [2.59–85.6], $p = .002$) for AKI; 7.5 (95% CI: [1.56–36.17], $p = .012$) for SuppO2; 11.88 (95% CI: [2.24–63.11], $p = .004$) for ICUStay and 32.8 (95% CI: [3.04–354.36], $p = .004$) for mortality. Lung infiltrates at presentation were associated with an OR of 14.8 (95% CI: [2.78–78.71], $p = .002$) for requiring SuppO2; 26 (95% CI: [4.23–159.91], $p < .001$) for requiring ICU stay; and 10 (95% CI: [1.38–72.74], $p < .023$) for mortality. Interval to Sotrovimab ≥4 days from symptom onset was associated with an OR of 7.5 (95% CI: [1.56–36.17], $p = .012$) for requiring SuppO2: 55.6% required SuppO2 if interval to Sotrovimab was ≥4 (versus 14.3% if <4 days). Finally, age ≥65 years and BMI >30 kg/m^2 were associated with mortality (OR 8.36 (95% CI: [1.18–59.44], $p = .034$) and 1.14 (95% CI: [1.01–1.29], $p = .037$), respectively. While multiple models were tested, the best fit model that demonstrated the lowest Akaike information criterion on a generalized linear model for that outcome is shown. Variables not included in that model for a dependent variable are identified by dashes. All analyses were performed using SPSS version 27. The ISARIC-4C score was not included in this multivariable regression model given the incorporation of blood urea nitrogen in the score and hence its collinearity with eGFR.

[k]Odds ratio (OR), the nonstandardized regression coefficient, the 95% confidence intervals (CIs), and *p*-values are shown.

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