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BRIEF COMMUNICATION

Breakthrough COVID-19 cases despite prophylaxis with 150 mg of tixagevimab and 150 mg of cilgavimab in kidney transplant recipients

Ilies Benotmane[1,2] | Aurélie Velay[2,3] | Gabriela Gautier-Vargas[1] | Jérôme Olagne[1] | Augustin Obrecht[1] | Noëlle Cognard[1] | Françoise Heibel[1] | Laura Braun-Parvez[1] | Nicolas Keller[1] | Jonas Martzloff[1] | Peggy Perrin[1] | Romain Pszczolinski[1] | Bruno Moulin[1,2] | Samira Fafi-Kremer[2,3] | Olivier Thaunat[4] | Sophie Caillard[1,2]

[1]Department of Nephrology, Dialysis and Transplantation, Strasbourg University Hospital, Strasbourg, France

[2]Inserm UMR S1109 Labex Transplantex, Fédération de Médecine Translationnelle, Strasbourg University, Strasbourg, France

[3]Department of Virology, Strasbourg University Hospital, Strasbourg, France

[4]Department of Transplantation, Nephrology and Clinical Immunology, Hospices Civils de Lyon, Edouard Herriot Hospital, Lyon, France

Correspondence
Ilies Benotmane, Department of Nephrology, Dialysis and Transplantation, Strasbourg University Hospital, 1 place de l'hôpital, Strasbourg 67091, France.
Email: ilies.benotmane@chru-strasbourg.fr

Abstract

The cilgavimab–tixagevimab combination retains a partial in vitro neutralizing activity against the current SARS-CoV-2 variants of concern (omicron BA.1, BA.1.1, and BA.2). Here, we examined whether preexposure prophylaxis with cilgavimab–tixagevimab can effectively protect kidney transplant recipients (KTRs) against the omicron variant. Of the 416 KTRs who received intramuscular prophylactic injections of 150 mg tixagevimab and 150 mg cilgavimab, 39 (9.4%) developed COVID-19. With the exception of one case, all patients were symptomatic. Hospitalization and admission to an intensive care unit were required for 14 (35.9%) and three patients (7.7%), respectively. Two KTRs died of COVID-19-related acute respiratory distress syndrome. SARS-CoV-2 sequencing was carried out in 15 cases (BA.1, $n = 5$; BA.1.1, $n = 9$; BA.2, $n = 1$). Viral neutralizing activity of the serum against the BA.1 variant was negative in the 12 tested patients, suggesting that this prophylactic strategy does not provide sufficient protection against this variant of concern. In summary, preexposure prophylaxis with cilgavimab–tixagevimab at the dose of 150 mg of each antibody does not adequately protect KTRs against omicron. Further clarification of the optimal dosing can assist in our understanding of how best to harness its protective potential.

KEYWORDS
clinical research/practice, infection and infectious agents—viral, infection and infectious agents—viral: SARS-CoV-2/COVID-19, infectious disease, solid organ transplantation

1 | INTRODUCTION

Transplant recipients are at high risk of COVID-19-related death.[1] Currently, the serum SARS-CoV-2 neutralizing capacity is considered the most reliable correlate of protection in this vulnerable population.[2] However, due to therapeutic immunosuppression, a significant fraction of transplant recipients fail to mount a protective antibody response despite reinforced

Abbreviations: BAU, binding arbitrary units; COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; KTRs, kidney transplant recipients; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 1 General characteristics of kidney transplant recipients ($n = 39$) who developed COVID-19 after preexposure prophylaxis with tixagevimab and cilgavimab

Patient #	Sex	Age (y)	Time elapsed from KT (y)	eGFR (ml/min/1.73 m^2)	Cardiovascular disease	Diabetes	Hypertension	BMI	History of rejection	CNI	MMF/MPA	Steroids	imTOR	Belatacept	Rituximab
2	M	72.3	1.1	33	0	0	1	27.4	0	0	1	1	0	1	0
3	F	60.1	4.6	35	0	1	1	19	1	TAC	1	0	0	0	0
35	M	57.5	0.19	71	0	0	1	26.5	0	TAC	1	1	0	0	0
7	M	60.2	1.5	50	0	1	1	27.1	0	TAC	1	1	0	0	0
34	F	56.2	13.3	45	0	0	1	29.1	0	CSA	1	0	0	0	0
13	M	73.4	0.24	35	1	0	1	29	0	TAC	1	1	0	0	0
30	F	71.6	1.1	24	0	0	1	29.6	0	0	1	1	0	1	0
33	M	79.6	1.4	19	1	0	1	24.1	0	TAC	0	1	0	0	0
36	M	75.4	7.4	28	1	1	1	24.3	0	TAC	1	1	0	0	0
18	M	74.6	4.4	36	1	0	0	24.9	1	0	1	1	0	1	0
21	M	62.0	10.6	60	1	1	0	31.3	0	TAC	1	1	0	0	0
22	M	67.9	2.6	26	1	1	1	21.7	0	0	1	1	0	1	0
23	M	68.9	2	14	1	1	1	34.1	0	CSA	0	1	0	0	0
24	F	74.3	8.7	18	1	0	1	29.2	1	CSA	1	1	0	0	0
1	M	48.46	0.1	51	0	1	1	30.7	0	TAC	1	1	0	0	0
4	F	23.3	1.6	98	1	1	1	20	0	TAC	1	1	0	0	0
5	M	56.0	4.8	66	0	1	1	29.6	0	CSA	1	0	0	0	0
6	F	77.6	12.9	59	0	1	1	27.4	0	TAC	1	1	0	0	0
8	F	38.5	18.2	31	0	0	0	22	1	TAC	1	1	0	0	0
9	M	29.5	7.3	60	0	0	1	20.4	1	0	1	1	0	1	0
10	M	51.9	3.17	59	0	0	1	17.6	1	TAC	1	1	0	0	0
11	F	72.8	3.2	56	0	0	1	19.2	0	TAC	1	1	0	0	0
12	M	63.4	1.1	33	1	0	1	30.3	1	0	1	1	0	1	0
14	M	38.7	32.9	49	0	0	0	24.6	1	TAC	1	1	0	0	0
27	M	61.3	3.8	58	0	0	0	22.5	0	TAC	1	1	0	0	0
28	F	70.0	1.6	25	0	0	1	26.1	1	TAC	1	1	0	0	0
29	F	57.7	4.7	46	0	1	1	31.9	1	TAC	1	1	0	0	0
31	M	51.3	2.2	46	1	0	1	32	0	0	1	1	0	1	0
32	F	72.4	1.5	37	0	0	1	18	0	TAC	1	0	0	0	0
38	F	51.3	14	61	1	1	1	32.5	1	TAC	1	1	0	0	0
39	M	63.9	16.5	50	0	0	1	33.5	0	TAC	1	1	0	0	0
15	F	79.8	1.1	82	0	0	1	31.6	0	TAC	1	1	0	0	0
16	M	52.8	4.3	56	1	0	1	22.8	0	TAC	1	1	0	0	0
19	M	56.0	4.6	36	1	1	1	26.4	0	CSA	1	1	0	0	0
20	M	49.0	2.3	24	0	1	1	38.4	1	0	1	1	0	1	0
37	F	56.2	1.5	55	1	1	1	28.2	1	TAC	1	1	0	0	0
25	M	56.0	2.9	31	0	1	1	28.39	0	TAC	1	1	0	0	0
26	F	53.5	2.6	44	0	0	1	20.9	0	TAC	1	1	0	0	0
17	F	19.7	2.3	87	0	0	1	29	0	TAC	1	1	0	0	0

Note: Orange background: hospitalized patients; yellow background: symptomatic patients managed out of hospital; white background: asymptomatic patient.

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitor; CSA, cyclosporine; d, days; eGFR, estimated glomerular filtration rate; F, female; HA, hospital admission; ICU, intensive care unit; KT, kidney transplantation; M, male; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; NA, not available; TAC, tacrolimus; y, years.

*Patients who did not receive casirivimab–imdevimab prior to cilgavimab–tixagevimab; **Patients who received casirivimab–imdevimab prior to cilgavimab–tixagevimab (uninterpretable anti-RBD IgG levels).

T depleting therapy	Number of vaccine doses	Time from casirivimab–imdevimab injection to cilgavimab–tixagevimab injection (d)	Time from last dose vaccine injection to COVID-19 (d)	Time from cilgavimab–tixagevimab injection to COVID-19(d)	Upper respiratory symptoms	Fever, headache, myalgia, chills	Lower respiratory symptoms	HA	ICU	Death	Variant	IgG RBD (BAU/mL)	Neutralizing capacity against Omicron BA.1
0	3	28	160	16	No	Yes	Yes	Yes	Yes	Yes	BA1.1		
NA	3	138	263	5	Yes	No	No	Yes	No	No			
1	4	*	162	57	Yes	No	Yes	Yes	No	No		2771**	Negative
0	4	71	214	35	No	Yes	Yes	Yes	No	No			
0	2	*	229	62	Yes	Yes	No	Yes	No	No		522	
0	3	*	141	30	No	Yes	No	Yes	No	No		1775	Negative
0	3	28	222	28	Yes	Yes	No	Yes	Yes	Yes	BA.1	5128**	
0	3	28	273	16	Yes	Yes	No	Yes	No	No			
0	3	51	252	32	No	Yes	Yes	Yes	No	No	BA1.1	2785	
0	3	26	306	42	Yes	Yes	No	Yes	No	No	BA1.1	9442**	Negative
1	3	41	152	26	Yes	No	No	Yes	Yes	No	BA.1		
1	2	28	280	12	Yes	Yes	No	Yes	No	No	BA1.1		
0	2	51	351	36	No	Yes	Yes	Yes	No	No	BA.1	4241**	Negative
1	3	62	190	22	No	Yes	Yes	Yes	No	No	BA.1	3786**	Negative
0	2	*	327	5	No	Yes	Yes	No	No	No	BA1.1	2458	Negative
0	3	57	276	10	No	Yes	Yes	No	No	No	BA1.1	10932**	Negative
1	3	84	265	18	Yes	Yes	No	No	No	No			
1	3	*	257	5	No	Yes	No	No	No	No	BA1.1	1790	Negative
1	4	51	207	9	Yes	Yes	No	No	No	No			
1	3	33	228	12	Yes	No	No	No	No	No			
1	3	23	291	37	Yes	Yes	No	No	No	No		6800**	Negative
0	3	108	265	36	Yes	No	No	No	No	No	BA.1	5686**	Negative
0	3	63	201	12	Yes	No	No	No	No	No			
NA	4	*	167	21	Yes	Yes	No	No	No	No		3420	Negative
0	4	*	49	5	Yes	Yes	No	No	No	No			
0	3	*	225	6	Yes	Yes	No	No	No	No			
1	3	28	243	12	Yes	Yes	No	No	No	No			
1	3	*	321	40	No	Yes	No	No	No	No		1581	
1	3	31	211	1	Yes	Yes	No	No	No	No		3570**	
1	3	*	302	22	Yes	No	No	No	No	No			
1	3	*	314	47	Yes	No	No	No	No	No			
1	3	*	93	9	Yes	Yes	No	No	No	No			
1	3	69	295	32	Yes	Yes	No	No	No	No	BA1.1	5182**	Negative
1	4	*	201	12	Yes	No	No	No	No	No			
0	2	41	222	4	No	Yes	No	No	No	No	BA1.1		
0	3	56	288	46	Yes	No	No	No	No	No	BA.2	5212**	
1	3	77	259	20	No	Yes	No	No	No	No			
1	2	30	230	34	Yes	Yes	No	No	No	No			
0	3	*	82	6	No	No	No	No	No	No			

vaccination schemes.[3,4] In this scenario, the use of anti-SARS-CoV-2 monoclonal antibodies for preexposure prophylaxis has recently gained traction. The casirivimab–imdevimab combination has been shown to confer satisfactory protection against the delta variant.[5,6] However, both casirivimab–imdevimab and other antibodies have limited neutralizing activity against the current variants of concern (omicron sublineages BA.1, BA.1.1 and BA.2). In contrast, the cilgavimab–tixagevimab combination retains a partial in vitro neutralizing activity against omicron.[7–9] Based on these data, health authorities have authorized the use of cilgavimab–tixagevimab for preexposure prophylaxis in immunocompromised patients with a weak anti-SARS-CoV-2 antibody response after vaccination. However, the amount of clinical protection provided by this strategy remains poorly understood as clinical trials on cilgavimab–tixagevimab were undertaken before the emergence of omicron.[10] In this study, we report a case series of kidney transplant recipients (KTRs) who developed the omicron infection despite preexposure cilgavimab–tixagevimab administration.

2 | PATIENTS AND METHODS

2.1 | Study population

All procedures and visits occurred at the Strasbourg and Lyon University Hospitals (France). Intramuscular gluteal prophylactic injections of 150 mg tixagevimab and 150 mg cilgavimab were offered as of December 28, 2021. This dosage was in accordance to the Food and Drug Administration (FDA) and European Medicines Agency regulations at the time of conduction of the study. All KTRs who showed a weak serological response to SARS-CoV-2 mRNA vaccines—defined by the French health authorities as an antibody titer below 264 BAU/ml—were eligible to receive cilgavimab–tixagevimab.[11,12] Patients who had already received the casirivimab–imdevimab combination (i.e., non-responders to vaccination with an antibody titer below 1 BAU/ml) were not excluded since these antibodies are not protective against the omicron variant and its sublineages.

The date of last follow-up was March 13, 2022. The diagnosis of COVID-19 was based on RT-PCR of nasopharyngeal swabs and genome sequencing was performed when suitable samples were available. The anti–receptor-binding domain (RBD) IgG response and neutralizing activity against the omicron BA.1 variant were assessed within the first 30 days after cilgavimab–tixagevimab injection and no later than the first 7 days after the onset of COVID-19.

2.2 | SARS-CoV-2 serological assessment

Anti-RBD IgG antibodies were detected by a chemiluminescence technique using the SARS-CoV-2 IgG II Quant commercial assay (Abbott Architect). A titer above 7.1 BAU per mL (50 arbitrary units per ml) was defined as a positive cutoff. The clinical sensitivity and specificity of this test are 98.3% (90.6%–100.0%) and 99.5%, respectively.[13] The indication to perform serologic screening was identical in all kidney transplant recipients followed in our outpatient clinic, that is, at 1 month after the last vaccine dose (M1), followed by M3 and M6. Serology assessments were also undertaken on the day of preexposure prophylaxis with monoclonal antibodies and 1 month thereafter.

2.3 | Neutralizing antibody assessment

Neutralizing antibody titers were measured with an in-house viral pseudoparticle-based assay, as previously described.[2] In brief, serum samples were sequentially diluted (from 1:40 to 1:1280) and incubated with BA.1 variant spike-pseudotyped lentiviral particles for 1 h at 37°C. Subsequently, this solution (100 µl) was added to 60%–80% confluent HEK293T-ACE2 cells (kindly provided by the O. Schwartz Laboratory, Institut Pasteur) seeded in 96-well plates. After 72 h, the Bright-Glo luciferase assay substrate (Promega) was added to each well and the luminescence was measured by a luminescence counter MicroBetaTriLux 1450LSC (Perkin Elmer). Results were expressed as the $\log_{10}$ of the sample dilutions that yielded 50% inhibition of pseudoparticle infectivity ($\log_{10}$ IC50). The neutralization efficiency—expressed as the $\log_{10}$ of the median half-maximal effective dilution (ED50)—was calculated using GraphPad Prism 9.3.1 (GraphPad Inc.). Sera were considered positive if they were able to neutralize more than 50% SARS-CoV-2 pseudovirus at a 1:40 dilution.

2.4 | Statistical analysis

Continuous data are presented as medians and interquartile ranges (IQRs) and differences were analyzed using the non-parametric Mann–Whitney *U* test. Categorical variables are expressed as counts and percentages and their analysis was conducted with the Fisher's exact test. All calculations were performed using GraphPad Prism 9.3.1 (GraphPad Inc.), with all tests two-sided at a 5% level of significance.

3 | RESULTS

Of the 416 KTRs who received prophylactic injections of cilgavimab–tixagevimab, 39 (9.4%) developed COVID-19 (Table 1). The patient characteristics are summarized in Table 2. They were mainly men (n = 23, 59%) with a median age of 60.1 years (IQR: 52.3–71.9 years). Most of them were treated with calcineurin inhibitors (n = 31, 84%), mycophenolate mofetil/mycophenolic acid (n = 37, 95%), and steroids (n = 37, 95%). Only one patient was treated with T-depleting therapies; however, none received

TABLE 2 General characteristics of the study patients according to the hospitalization status

	Total cohort ($n = 39$)	Not hospitalized ($n = 25$)	Hospitalized ($n = 14$)	p
Age (years)	60.1 [52.3; 71.9]	56.0 [49.0; 63.4]	70.2 [60.7; 74.1]	**<.01**
Male	23 (59%)	13 (52%)	10 (71%)	.24
BMI (kg/m^2)	27.4 [22.6; 30.0]	27.4 [22; 30.7]	27.2 [24.5; 29.2]	.9
eGFR (ml/min/1.73 m^2) median	46.0 [32.0; 58.5]	51.0 [36.6; 59.0]	34.0 [24.5; 42.8]	**<.01**
Cardiovascular disease	15 (38%)	7 (28%)	8 (57%)	.073
Diabetes	16 (41%)	10 (40%)	6 (43%)	.86
Hypertension	34 (87%)	22 (88%)	12 (86%)	1
Time elapsed from KT (years)	2.90 [1.50; 6.05]	3.17 [1.60; 4.80]	2.30 [1.18; 6.70]	.37
History of rejection	13 (33%)	10 (40%)	3 (21%)	.3
Number of vaccine doses				
2	6 (15%)	3 (12%)	3 (21%)	.87
3	27 (69%)	18 (72%)	9 (64%)	-
4	6 (15%)	4 (16%)	2 (14%)	-
T depleting therapy at induction	19 (51%)	15 (62%)	4 (31%)	.065
CNI				
Tacrolimus	26 (67%)	19 (76%)	7 (50%)	.31
Cyclosporine	5 (13%)	2 (8%)	3 (21%)	-
No	8 (21%)	4 (16%)	4 (29%)	-
MMF/MPA	37 (95%)	25 (100%)	12 (86%)	.12
mTOR inhibitor	0	0	0	
Belatacept	8 (21%)	4 (16%)	4 (29%)	.42
Steroids	35 (90%)	23 (92%)	12 (86%)	.61
SARS-CoV-2 variant				
BA1.1	9 (60%)	5 (71%)	4 (50%)	.28
BA.1	5 (33%)	1 (14%)	4 (50%)	-
BA.2	1 (6.7%)	1 (14%)	0 (0%)	-
Time elapsed from tixagevimab-cilgavimab injection (days)	20.0 [9.50; 34.5]	12.0 [6.00; 32.0]	29.0 [17.5; 35.8]	**.04**
ICU	3 (7.7%)	0 (0%)	3 (21%)	**.04**
Death	2 (5.1%)	0 (0%)	2 (14%)	.12

Note: Data are expressed as median (interquartile range) or *n* (%).

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin.

rituximab during the previous year. In addition, none of them had a previous history of symptomatic COVID-19. All had been previously vaccinated against SARS-CoV-2 with an mRNA-based vaccine (22 with the mRNA-1273 vaccine, 15 with the BNT162b2 vaccine, and 2 with both) but failed to develop a protective humoral response. Three were vaccinated before transplantation and the remaining 36 thereafter. The time interval between the last vaccine dose and the serology measurement ranged from 39 days to 322 days. The time interval from the receipt of the most recent vaccine dose to COVID-19 infection ranged from 49 days to 351 days. From August 17, 2022, to December 22, 2022, a total of 25 patients were treated with casirivimab–imdevimab. The time interval between casirivimab–imdevimab and tixagevimab–cilgavimab administration ranged from 23 days to 138 days. The median time elapsed from cilgavimab–tixagevimab injections to the onset of COVID-19 was 20 days (IQR: 9.5–34.5 days). With the exception of one patient, all KTRs were symptomatic. Hospitalization was required for 14 patients (35.9%) of whom three were transferred to intensive care unit. Two KTRs died of COVID-19-related acute respiratory distress syndrome. Compared with cases managed on an outpatient basis, hospitalized patients were older (median: 70.2 years vs. 56 years, respectively, $p < .01$), had a lower estimated glomerular filtration rate (median: 34 ml/min/1.73 m^2 vs. 51 ml/min/1.73 m^2, respectively,

$p < .01$), and a longer time elapsed from cilgavimab–tixagevimab injection (median: 29 days vs. 12 days, respectively, $p = .04$, Table 2). SARS-CoV-2 sequencing was carried out in 15 cases (BA.1, $n = 5$; BA.1.1, $n = 9$; BA.2, $n = 1$). Viral neutralizing activity of the serum was negative in the 12 tested patients (five hospitalized patients and seven managed in an outpatient setting), suggesting that this prophylaxis strategy does not provide sufficient protection against this SARS-CoV-2 variant of concern. Five patients had anti-RBD IgG titers <3500 BAU/mL. In the remaining seven patients, preexisting casirivimab–imdevimab administration did not allow interpreting anti-RBD IgG levels.

4 | DISCUSSION AND CONCLUSIONS

In this study, we describe the occurrence of severe omicron infections despite prophylactic administration of cilgavimab–tixagevimab. Notably, two study participants died of COVID-19. Previous investigations have shown that the BA.1.1 subvariant is characterized by a higher in vitro resistance to cilgavimab–tixagevimab compared with the BA.1 variant.[8,9] The former genotype was predominant in our cohort, which can at least in part explain the disappointing level of protection observed in these patients. However, this issue is unlikely to be the only explanation for our findings; accordingly, we also observed that none of the sera collected after administration of cilgavimab–tixagevimab was able to neutralize the BA.1 variant in vitro. These results suggest that intramuscular injections of a combination of 150 mg tixagevimab and 150 mg cilgavimab might not be sufficient to elicit protective levels of circulating anti-RBD antibodies. Our data are in accordance with those obtained in a cohort of 63 KTRs who did not develop COVID-19;[14] in this sample, only 9.5% of all participants was able to neutralize the omicron variant 1 month after cilgavimab–tixagevimab administration. This percentage was markedly lower than that observed in patients who had been previously infected with SARS-CoV-2 (71%; 10/14).[14]

Our clinical findings confirm recent FDA recommendations, derived from in vitro models, underlining the necessity to increase the dose of cilgavimab–tixagevimab™.[8] However, the European Medicines Agency is still recommending a dose of 150 mg for each antibody. Information on the effectiveness of higher antibody doses would have been interesting; however, as an increased dosage is not currently recommended, we are unable to provide these data. Further pharmacokinetic studies are warranted to determine the optimal dose of cilgavimab–tixagevimab for primary prophylaxis of COVID-19. Additional research is also required to investigate whether an increased tixagevimab–cilgavimab dosage would be sufficient to protect immunocompromised patients against the omicron variant and its sublineages. Under these circumstances, KTRs should be advised to maintain strict sanitary protection measures and receive booster doses.

DISCLOSURE

Sophie Caillard and Olivier Thaunat received consulting fees from Astra Zeneca. All other authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data supporting the findings from this study are available from the corresponding author upon reasonable request.

ORCID

Ilies Benotmane https://orcid.org/0000-0001-9113-2479
Gabriela Gautier-Vargas https://orcid.org/0000-0001-9377-1055
Jérôme Olagne https://orcid.org/0000-0001-6792-5399
Noëlle Cognard https://orcid.org/0000-0001-6602-2059
Samira Fafi-Kremer https://orcid.org/0000-0003-3886-7833
Olivier Thaunat https://orcid.org/0000-0002-3648-8963
Sophie Caillard https://orcid.org/0000-0002-0525-4291

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