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Occurrence of Severe SARS-CoV-2 Infection in Fully Vaccinated Solid Organ Transplant Recipients

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ABSTRACT

The present study presents the clinical outcome of SARS-CoV-2 disease in relation to the humoral response in fully vaccinated solid organ transplant (SOT) recipients. Our patient cohort consists of 455 SOT recipients, vaccinated with one of the 2 approved mRNA vaccines. The antibody response was measured 1 month after the second dose, and previously infected patients have been excluded. Of the 449 remaining patients, 15 (3.34%) tested positive, using SARS-CoV-2 polymerase chain reaction. Their mean age was 43.7 ±14.4 years, and median time from transplantation was 7.8 years (1.2-30.2). Eleven patients (73.3%) had been vaccinated with BNT162b2 and 4 (26.7%) with the mRNA1273 vaccine. At the time of infection 9 (60%) patients had a negative (<50 AU/mL) antibody titer, and 6 (40%) had a positive one (>50 AU/mL). Median antibody titer, 27.4± 14.0 days after the second dose, measured at 13 AU/mL (0-7480 AU/mL). Renal function did not appear to be affected by the disease. The mean estimated glomerular filtration rate at diagnosis was 48 ± 15 mL/min, and when in a 29-day (1-101) median follow-up was 53.9± 20.9 mL/min. Of the 15 patients, 7 had mild symptoms and were not hospitalized, and of the remaining 8 (53.3%) who needed hospitalization 7 had severe disease and 2 of them expired. The study confirms the variable and often severe course of coronavirus 2019 infection in SOT recipients, even after their full vaccination, highlighting the need to vaccinate their close relatives and to accelerate the implementation of the booster dose of vaccine.

SOLID organ transplant (SOT) recipients represent a high-risk group for all SARS-CoV-2 infection-related adverse outcomes, with early case fatality rates approaching 20% that have been reported [1]. However, they have been excluded from all phase 3 vaccination trials.

After their prioritization for coronavirus 2019 (COVID-19) vaccination in most countries, there is increasing evidence about alarmingly low response rates to both mRNA vaccines. In a recently published systematic review, the pooled estimate of antibody response after full vaccination in SOT recipients was at 35% [2].

Notably, regarding humoral response to the SARS-CoV-2 vaccines, even compared with other immunocompromised patient groups, SOT recipients perform worse. In a recent study by Haidar et al, among different immunosuppressive conditions, seropositivity was the lowest in SOT recipients, 37.2% compared with 54.7% and 82.4% in patients with hematologic malignancies and solid tumors, respectively [3].

Most disturbingly, besides reduced immunogenicity to vaccinations, as already known by other vaccines, lifelong immunosuppression is associated with suboptimal immune response to viral pathogens [4].

The first reports about occurrence of COVID-19 infection with variable and often severe disease course in SOT recipients after full vaccination have been published [5], implicating the urgent need for more data.

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MATERIAL AND METHODS

The present study assessed the disease course and the clinical outcomes of SARS-CoV-2 infection in relation to humoral response after full vaccination with one of the 2 mRNA SARS-CoV-2 vaccines in 15 out of a large cohort of 449 SOT recipients.

Our patient cohort consisted of 455 consecutive SOT recipients who have been vaccinated with one of the mRNA SARS-CoV-2 vaccines. The majority of them, 372 out of 456 (81.6%), were kidney transplant recipients who are all actively under follow up at the Clinic of Nephrology and Renal Transplantation at Laiko Hospital of Athens. The 14 liver transplant recipients are under follow up at the Hepatology Unit of the same Hospital and the 48 and 22 heart and lung recipients are under follow up at the Onassis Cardiac Surgery Center of Athens, respectively.

All SOT recipients had received 2 doses of either the BNT162b2 (307 patients, 67.3%) or the mRNA1273 (149 patients, 32.7%) vaccine.

Antibodies were measured at a median of 28.5 days after the second vaccination dose (range, 22-33 days) using a chemiluminescent microparticle immune assay (CMIA), which quantifies IgG antibodies against the receptor-binding domain of the S1 subunit of the spike protein of SARS-CoV-2 (Abbott SARS-CoV-2 IgG II Quant). The linear range of the assay is between 21.0 and 40, 000AU/mL, and according to the manufacturer the clinical specificity is estimated at 99.55% (95% confidence interval [CI] 99.15%-99.76%) and the clinical sensitivity at 98.81% (95% CI 93.56%-99.94%) in samples collected ≥ 15 days after a positive polymerase chain reaction (PCR) at a cut-off value of 50 AU/mL. Anti-SARS- CoV-2 receptor-binding domain IgG assays have shown an excellent correlation with neutralizing antibodies.

Additionally, samples were tested for IgG antibodies directed against the SARS-CoV-2 nucleocapsid (N) protein, indicative of previous infection, using the Abbott SARS-CoV-2 IgG kit on an Architect i2000SR analyzer (Abbot Diagnostics, Lake Forest, IL) according to manufacturer's instructions. An index [sample/calibrator (S/C)] cutoff of 1.4 was used. Patients testing positive for anti-N Abs (6 in total, 1.7%) were excluded from further analysis [6,7].

From the remaining 449 SOT recipients, 15 tested positive for SARS-CoV-2 PCR at the time of infection.

Clinical data about the transplantation status, immunosuppression, comorbidities, and concomitant medications were obtained from the patients' medical charts. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Because all SOT recipients are actively followed and hospitalized, if necessary, in the transplant unit of either of the 2 reference hospitals of Athens, it is highly unlikely that a transplanted patient with a serious problem such as a positive PCR test for SARS-COV-2 could be missed. Furthermore, most of them underwent PCR testing for various reasons —as in Greece, it is mandatory for several activities, even after full vaccination. Even those who were asymptomatic followed the advice to contact their transplant physicians, which are all working in the 2 abovementioned hospitals. After a positive PCR they were treated as outpatients with laboratory and clinical evaluation once to twice a week. The study was approved by the Ethics committee of the Onassis Cardiac Surgery Center.

DEFINITIONS OF DISEASE SEVERITY

According to the FDA, mild disease was characterized by fever, cough, malaise, myalgias, anosmia and ageusia, and other less common symptoms (ie, from gastrointestinal tract as nausea, vomiting, or diarrhea in the absence of low respiratory tract involvement). Moderate disease included lower respiratory tract involvement with infiltrates on chest imaging without dyspnea or hypoxia. Severe disease was defined as presence of lung infiltrates with hypoxia—oxygen saturation at room air less than 94% and/or need for oxygen supplementation or ventilator support.

RESULTS

Breakthrough infection, defined as positive SARS-CoV-2 PCR more than 14 days after completion of the second vaccination dose, occurred in 15 out of 449 (3.34%) recipients, 13 kidney, one heart, and one kidney-heart recipient, respectively. Twelve out of 15 patients (80%) were male and 3 (20%) were female. Mean age of infected patients was 43.7 ±14.4 years and median time from transplantation 7.8 years (1.2-30.2). From the 15 SOT recipients, 11 (73.3%) had received the BNT162b2 and 4 (26.7%) the mRNA1273 vaccine. At the time of infection, 6 out of 15 patients (40%) had mounted positive response, and 9 patients (60%) had negative response with antibody titers below the threshold of 50 AU/mL. Median antibody titer measured at a mean of 27.4± 14.0 days from the second vaccination dose in all 15 patients was 13 AU/mL (0-7480 AU/mL). Mean time from the first dose until infection was 107.0 ± 32.6 days and from the second dose 81.8 ± 31.2 days, respectively. Renal function was well preserved—creatinine at the time of infection was 1.7 ± 0.4mg/dL with an eGFR calculated with the Chronic Kidney Disease Epidemiology Collaboration equation of 48 ± 15 mL/min. Median creatinine peak during hospitalization was 1.99 mg/dL (1.3-3.8) and mean eGFR dropped to 42.8 ± 15.7 mL/min. After a median follow up of 29 days (1-101) creatinine returned to the preadmission values to 1.4mg/dL (1.07-2.6) and mean eGFR to 53.9± 20.9mg/dL.

As depicted in Table 1, at least one comorbidity was present in all SOT recipients. All were transplanted for more than 1 year and received stable maintenance immunosuppression. In the 13 kidney transplant recipients, modification of immunosuppression at the time of COVID-19 infection consisted of withdrawal of the antimetabolite and reduction of tacrolimus with target levels below 6 ng/mL, and in the one heart and the 2 kidney-heart recipients tacrolimus was reduced without withdrawal of the antimetabolite. In those who recovered, immunosuppression was gradually restored to preinfection levels after 3 weeks. Treatment for COVID-19 comprised of prophylactic dose of low-molecular weight heparin for 1 month to all, regardless of disease severity. Broad-spectrum antibiotics were administered to 5 patients with elevated markers of inflammation and dexamethasone and the antiviral remdesivir to the 7 patients with severe disease.

Disease severity was categorized according to the FDA definitions. Disease course was variable: out of the 15 infected patients, 7 had minimal symptoms or mild disease and were not hospitalized. Eight of the 15 recipients (53.3%) were hospitalized: one had moderate and 7 had severe disease. From those, 2 developed life-threatening disease; the first developed severe respiratory insufficiency, was intubated and expired in the intensive care unit from sepsis, and the second patient was a

Table 1. Clinical Characteristics of Solid Organ Transplant Recipients Who Developed SARS-CoV-2 Infection After Vaccination

	Organ	Age	Gender	Maintenance	Comorbidities	Baseline eGFR (CKD-EPI)	SARS-CoV-2 Vaccine	Antibodies Positivity	Antibodies Titer	Years From Tx To First Positive PCR Test	Days From 2nd Dose to First Positive PCR Test	Severity of COVID-19	Treatment for COVID-19	Modification in Immuno-suppression	Hospitali-zation	Days of Hospitali-zation	Follow-up Days	Follow-up eGFR (CKD-EPI)
1	Heart	36,53	M	TAC, EVER	Obesity, CVD, HTN	59	Pfizer	Yes	50,8	8,78	35	Severe	Antibiotics, LMWH, DEXA, remdesivir	FK<6	1	57	69	DIALYSIS
2	Kidney	40,69	M	TAC, MMF, MP	Obesity, HTN	57	Pfizer	No	10,3	3,34		Severe	DEXA, remdesivir, LMWH	Withdrawal MMF, FK<6	1	6	101	74
3	Heart-kidney	37,04	F	AZA, TAC, MP	HTN, CVD	33	Pfizer	No	13,1	30,17	9	Mild (asymptomatic)	LMWH	FK<6	0	0	46	31
4	Kidney	58,58	M	TAC, MMF, MP	HTN	55	Pfizer	No	0	8,54	57	Mild	LMWH	Withdrawal MMF, FK<6	0	0	27	64
5	Kidney	65,72	M	TAC, MMF, MP	HTN	36	Pfizer	No	3,2	9,75	115	Severe	LMWH, antibiotics, IVIG, tocilizumab, DEXA, remdesivir	Withdrawal MMF, FK<6	1	26	28	ICU
6	Kidney	53,24	F	CsA, MMF, MP	HTN	28	Pfizer	No	2,1	15,66	74	Moderate	LMWH	Withdrawal MMF	1	11	30	20
7	Kidney	27,81	M	TAC, MMF, MP	HTN	77	Moderna	Yes	694,2	2,41	73	Mild	LMWH	Withdrawal MMF, FK<6	0	0	28	70
8	Kidney	44,79	M	TAC, MMF, MP	HTN, CVD, obesity	26	Moderna	No	0,9	1,33	76	Severe	LMWH, DEXA, remdesivir, antibiotics	Withdrawal MMF, FK<6	1	6	22	30
9	Kidney	29,64	M	TAC, MMF, MP	HTN, DM	45	Pfizer	No	4,6	1,45	87	Severe	LMWH, DEXA, remdesivir	Withdrawal MMF, FK<6	1	6	34	82
10	Kidney	50,39	M	CsA, MMF, MP	HTN, DM, CVD	60	Pfizer	No	0	3,10	95	Severe	LMWH, DEXA, remdesivir, antibiotics	Withdrawal MMF	1	20	36	81
11	Kidney	37,76	F	TAC, MMF, MP	HTN	40	Pfizer	No	0	6,39	97	Mild	LMWH	Withdrawal MMF, FK<6	0	0	30	55
12	Kidney	21,83	M	TAC, MMF, MP	HTN	41	Pfizer	Yes	7480	1,20	108	Mild	LMWH	Withdrawal MMF, FK<6	0	0	8	39
13	Kidney	32,71	M	TAC, MMF, MP	HTN	58	Moderna	Yes	371,9	7,91	113	Severe	LMWH, DEXA, remdesivir, antibiotics	Withdrawal MMF, FK<6	1	6	6	48
14	Kidney	72,82	M	TAC, MMF, MP	HTN	61	Pfizer	Yes	87,1	12,38	115	Mild	LMWH	Withdrawal MMF, FK<6	0	0	1	53
15	Kidney	46,26	M	TAC, MMF, MP	HTN	65	Moderna	Yes	4314,1	4,51	91	Mild (asymptomatic)	LMWH	Withdrawal MMF, FK<6	0	0		

AZA, azathioprine; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CsA, cyclosporine; CVD, cardiovascular disease; DEXA, dexamethasone; DM, diabetes mellitus; EVER, everolimus; F, female; HTN, hypertension; ICU, intensive care unit; IVIG, intravenous immunoglobulin; LMWH, low molecular weight heparin; M, male; MMF, mycophenolate mofetil; MP, methylprednisolone; TAC, tacrolimus; Tx, transplantation.

heart recipient who died after a long and complicated hospitalization from gram-negative sepsis. Median time of hospitalization was 9 days (6-57).

DISCUSSION

As feared by many transplant physicians, breakthrough infection is a major issue in SOT recipients and correlates with low or undetectable antibody titers. Most disturbingly, from the few data available, in transplanted patients, COVID-19 infection after full vaccination, does not seem to run a more indolent course [2].

The biggest cohort published until today by Caillard et al [8] included 55 patients after kidney and kidney-pancreas transplantation. Similar to ours, they also found a variable clinical course. Hospitalization rate in their cohort was lower at 27% compared with 53% in our study. From the 15 hospitalized patients in the French cohort, 6 were admitted to the intensive care unit and 3 out of 15 (20%) died. We found a case fatality rate of 25% (2 out of 8) among our hospitalized SOT recipients. Of course, numbers are too small to draw definite conclusion, but they are indicative of an unpredictable and often fatal disease course. Regarding immunogenicity, in the French study, only one patient among the 25 in whom antibody titers were available had positive titers. In our study, antibody positivity was present in 40% of SOT recipients (6 out of 15) but with low titers.

The weak immune response and the unpredictable disease course of breakthrough infection has already prompted some National Health Authorities as the French to recommend a third vaccination dose in SOT recipients with the first studies reporting safety and improved immunogenicity after administration of the booster dose [9,10].

The present study indicates a variable and often severe disease course of COVID-19 infection in transplanted patients, even after full vaccination. We found a rate of breakthrough infection of 3.34% with numbers of infected SOT recipients growing every day. Unfortunately, we also recorded a variable, often severe, and even fatal disease course among infected individuals.

These findings, besides continuous practice of safety measures and "cocooning" vaccination of their close relatives, strongly implicate reevaluation of the vaccination policy with rapid implementation of the booster dose, as is already approved in many countries including ours.

REFERENCES

[1] Marinaki S, Tsiakas S, Korogiannou M, Grigorakos K, Papalois V, Boletis I. A systematic review of COVID-19 infection in kidney transplant recipients: a universal effort to preserve patients' lives and allografts. J Clin Med 2020;9:2986.

[2] Carr EJ, Kronbichler A, Graham-Brown M, Abra G, Argyropoulos C, Harper L, et al. Review of early immune response to SARS-CoV-2 vaccination among patients with CKD. Kidney Int Rep 2021;6:2292–304.

[3] Haidar G, Agha M, Lukanski A, Linstrum K, Troyan R, Bilderback A, et al. Immunogenicity of COVID-19 vaccination in immunocompromised patients: an observational, prospective cohort study interim analysis, https://www.medrxiv.org/content/; 2021 [accessed 10.11.21].

[4] Eckerle I, Rosenberger KD, Zwahlen M, Junghanss T. Serologic vaccination response after solid organ transplantation: a systematic review. PLoS One 2013;8:e56974.

[5] Malinis M, Cohen E, Azar MM. Effectiveness of SARS-CoV-2 vaccination in fully vaccinated solid organ transplant recipients. Am J Transplant 2021;21:2916–8.

[6] Perkmann T, Perkmann-Nagele N, Breyer M-K, Breyer-Kohansal R, Burghuber OC, Hartl S, et al. Side by side comparison of three fully automated SARS-CoV-2 antibody assays with a focus on specificity. Clin Chem 2020:hvaa198.

[7] Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, et al. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. N Engl J Med 2021;385:e84.

[8] Caillard S, Chavarot N, Bertrand D, Kamar N, Thaunat O, Moal V, et al. Occurrence of severe COVID-19 in vaccinated transplant patients. Kidney Int 2021;100:477–9.

[9] Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. N Engl J Med 2021;385:661–2.

[10] Benotmane I, Gautier G, Perrin P, Olagne J, Cognard N, Fafi-Kremer S, et al. Antibody response after a third dose of the mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients with minimal serologic response to 2 doses. JAMA 2021;326:1063–5.