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Research article

Donor-directed immunologic safety of COVID-19 vaccination in renal transplant recipients

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ABSTRACT

Infection risk and COVID-19 outcomes make SARS-CoV-2 vaccination essential for solid-organ transplant recipients. Reports of immune activation after vaccination causing graft failure raise concerns, but data are limited. Here, we document graft function, donor-derived-cell-free-DNA(dd-cfDNA), and donor-specific antibodies (DSA) in solid-organ renal transplant recipients after vaccination.

Retrospective demographics, graft function, and immunologic parameters were collected in 96 renal transplant patients one month after their second vaccine dose. For-cause biopsies were performed based on clinician judgment.

Similar proportions of subjects experienced increases (39.6 %) and decreases (44.8 %) in serum creatinine in the post-vaccination period, $p = 0.56$. Similar proportions of subjects experienced increases (23 %) and decreases (25 %) in serum ddcfDNA in the post-vaccination period, $p = 0.87$. Post-vaccination changes in serum creatinine and ddcfDNA ($r(95) = -0.04$, $p = 0.71$), serum creatinine and cumulative DSA MFI ($r(95) = 0.07$, $p = 0.56$), and ddcfDNA and cumulative DSA MFI ($r(95) = 0.13$, $p = 0.21$) were not significantly correlated. Five subjects had increased cumulative DSA MFI, but there were no de novo cases. Biopsies on three subjects confirmed pre-existing diagnoses.

Our study found minimal evidence of donor-directed immunologic activity post-vaccination, and all immunologic changes did not correlate to graft dysfunction. We believe these findings do not amount to evidence of post-vaccination deleterious donor-directed activation. SARS-CoV-2 vaccination is immunologically safe and should continue for renal transplant recipients.

1. Introduction

Vaccination against SARS-CoV-2, especially with mRNA-based vaccines, proved to successfully induce anti-spike protein antibodies in clinical trials with a 95 % serologic conversion rate. [1–2] However, the low proportions of solid organ transplant recipients achieving seroconversion have raised doubts about the effectiveness of vaccination while leaving concerns about potential side effects. [3–5] Much effort has been put into achieving serologic conversion in transplant patients, including additional doses of vaccine and modulation of immunosuppression regimens. [6–10] Anecdotes of post-vaccination acute cellular rejection and IgA nephropathy exacerbations fuel fears of vaccine-induced immune activation triggering rejection. [11–12] While the association of infection, particularly viral, with rejection is well-known, efforts to establish a relationship between vaccination and rejection have remained controversial. [13–16] For instance, vaccination against influenza has been shown to decrease the risk of graft loss after kidney transplantation. [17] Due in part to pervasive worry about the deleterious effects of activating the immune system of transplant recipients, society guidelines still provide direct recommendations to

Abbreviations: DdcfDNA, Donor-derived-cell-free-DNA; DSA, Donor-specific antibodies; MFI, Mean fluorescence intensity; IQR, Inter-quartile range.

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physicians about the safety of vaccination post-transplant. [18] Here, we aimed to document the donor-directed immunologic consequences of vaccination for SARS-CoV-2 as measured by graft function, donor-derived-cell-free-DNA (dd-cfDNA), and donor-specific antibodies (DSA) in a convenient sample of renal transplant recipients.Table 1a.

2. Methods

2.1. Patient selection

In this observational cohort study, sequential renal transplant recipients who had been vaccinated against SARS-CoV2 between December 2020 and July 2021 were evaluated during routine clinical follow-up. Retrospective demographic data, data on graft function, and routine immunologic parameters were collected.

2.2. SARS-CoV2 vaccination

At our center, we advise vaccination against SARS-CoV2 as soon as three months post-transplantation. Subjects received vaccination at either our institution or an outside facility with whichever vaccine was available at the time (Moderna, Pfizer, J&J). All patients in this series that received a two-dose regimen received the same dose both times. At the time of the study, booster doses were not yet authorized and therefore not evaluated in this study.

2.3. Immunologic evaluation

As part of the standard immunologic surveillance, donor-derived cell-free DNA (ddcfDNA; *AlloSure, CareDx*) and anti-HLA donor-specific antibodies (DSA; Single Antigen Bead testing, *One Lambda*) were collected approximately 30 days after the second (first with J&J) dose of vaccine. DSA with MFI < 1500 were excluded. Biopsies were performed for-cause based on clinician judgement, including elevated serum creatinine concentrations and elevated ddcfDNA values. A ddcfDNA cutoff of 1 % was chosen as clinically significant based on clinical institutional practices and previous studies documenting expected ranges and associations with acute rejection. [19–20] In patients with a post-vaccine positive percent change in ddcfDNA or those in whom a percent change was not able to be calculated, a follow up value was obtained at 60 days post-vaccination to document the trajectory of the rise.

2.4. Incidence of acute and chronic graft pathology in the pre-vaccine era

To assess for the baseline incidence of biopsy-proven acute and chronic allograft pathology, records for the five-year period between January 2016 and December 2020 were reviewed for all biopsies performed on transplanted kidneys at our institution. If there were multiple biopsies for a single patient, only the first biopsy was considered. Biopsies within the first year post-transplant were excluded. Those performed beyond five years post-transplant were also excluded in order to obtain an accurate incidence for the surveyed period. Biopsy results were reviewed as reported in the medical record and categorized as acute (rejection, acute tubular injury, acute TMA, necrosis, BK virus infection, infection pyelonephritis) or chronic (rejection, arteriosclerosis, fibrosis, glomerulosclerosis, BK nephropathy, chronic TMA). These numbers were compared to the number of kidney transplants performed yearly and the number of graft failures within the first year post transplant.

2.5. Statistics

Continuous variables were reported as medians and inter-quartile ranges (IQR) and compared using the Mann-Whitney *U* test. Contingency table analysis including the Fisher Exact test was used to compare categorical variables. Pearson correlation was used to determine relationships between continuous variables. Results were considered significant at a p-value < 0.05 and all reported p-values were two-sided.

3. Results

3.1. Patient selection

During the study period, 96 renal transplant recipients who underwent vaccination for SARS-CoV-2 were evaluated. The median (IQR) time between vaccination and transplant was 3.5 (6.7) years. Demographics are summarized in Table 1b, 2b, and 3b. Vaccination was with Moderna, Pfizer, and Johnson & Johnson/Jansenn in 36 %, 59 %, and 3 % of subjects, respectively.

Table 1a
Depicts patient outcomes for those with >1% ddcfDNA after second SARS-COV-2 vaccination.[b]

Summary of Patients with ddcfDNA Greater than 1%[a]							
Patient	[Cr] 30 days post-vaccine, mg/dl	% Change in [Cr]	% ddcfDNA post-vaccine	% Change ddcfdna	Follow-up ddcfdna %	Biopsy	Diagnosis/Intervention
M	0.96	-11%	2	53%	1.5		
F	2.04	-9%	1.2	0%	1.2		
K	0.79	-6%	2.3	...[c]	1.8		
I	0.83	-2%	1.1	12%	0.99		
E	1.06	-1%	1.6	90%	...		
N	1.12	-1%	2.11	46%	1.58		
P	1.34	-1%	1.4	...	...		
G	0.61	0%	2.1	...	1.8		
Q	0.78	3%	2.6	...	1.8		
L	0.77	8%	1.1	...	...		
O	1.75	9%	1.6	67%	0.99		
H	1.66	13%	5.7	-111%	4.2		
A	3.6	21%	6.4	67%	2.8	Yes	Chronic Active AMR
B	4.27	58%	1.2	...	0.71	Yes	Chronic TMA
J	1.46	...	1.8	...	1.6		

[a]ddcfDNA = donor-directed cell-free DNA, [Cr] = creatinine concentration, AMR = Antibody mediated rejection, TMA = Thrombotic Microangiopathy, AMR = antibody mediated rejection
[b]All subjects received the same vaccine for both doses
[c]Some data not available
[Note: Patient A and B required biopsies due to [Cr] > 1.7 mg/dL and ddcfDNA .1%]

Table 1b
Summary of Patients with Donor-Derived Cell-Free DNA Greater than 1%

Table 1b summarizes the characteristics and overall % change in immunologic parameters for the 15.6% (n = 15) of patients with ddcfDNA greater than 1 percent after second vaccination. [a]

Patient Characteristics	n = 15
Age at vaccination, median age (IQR)	49.6 (9.96)
Female Gender, n (%)	9 (60)
Txp: vaccine, median years (IQR)	3.02 (8.39)
Vaccine[b], n (%)	
Moderna	5 (33)
Pfizer	9 (6)
J&J	1 (7)
Immunosuppression, n (%)	
Tacrolimus	8 (53)
Mycophenolate Mofetil	15 (100)
Prednisone	11 (73)
Belatacept	3 (20)
Results, median (IQR)	
% Change DSA	35 (90.0)
% Change creatinine	-0.37 (13)
% Change ddcfDNA	49 (64)

[a]ddcfDNA = donor-directed cell-free DNA, Txp: vaccine = Years from transplant to first vaccine dose, DSA = Donor-specific antibodies, IQR = Interquartile range
[b]All subjects received the same vaccine for both doses

3.2. Immunosuppression

Induction immunosuppression was with thymoglobulin in 69 % (n = 66) of subjects. Anti-metabolite therapy with mycophenolic acid or azathioprine was used in 91 % (n = 87) of subjects. A calcineurin-sparing Belatacept-based regimen was used in 15 % (n = 14) of subjects. Immunosuppression regimens are summarized in Table 1b, 2b, and 3b.

3.3. Immunologic/graft evaluation

Post-vaccine labs were obtained a median (IQR) of 38 (22) days after vaccination.

Following vaccination, similar proportions of subjects experienced increases (n = 38, 39.6 %) and decreases (n = 43, 44.8 %) in serum creatinine compared to the pre-vaccine period, p = 0.56. Three subjects had a 0 % change in serum creatinine.

Following vaccination, similar proportions of subjects experienced increases (n = 22, 23 %) and decreases (n = 24, 25 %) in serum ddcfDNA compared to the pre-vaccine period, p = 0.87. Eleven subjects had a 0 % change in serum ddcfDNA. (Fig. 1).

Percent changes in serum creatinine and ddcfDNA were not significantly correlated (r(95) = -0.04, p = 0.71). Percent changes in serum creatinine and cumulative DSA MFI were not significantly correlated (r(95) = 0.07, p = 0.56). Percent changes in ddcfDNA and cumulative DSA MFI were not significantly correlated (r(95) = 0.13, p = 0.21). Post-vaccine ddcfDNA was greater than 1 % in 15.6 % (n = 15) of subjects (Table 1). Pre-vaccination DSA were present in 17 % of subjects. The cumulative DSA MFI increased post-vaccination in 5.2 % (n = 5) of subjects (Table 2). There were no cases of *de novo* DSA production.

There were three for-cause biopsies during the study period. One subject was biopsied for elevated creatinine (3.4 mg/dL, baseline 3.0 mg/dL) and ddcfDNA (1.2 %) and revealed chronic thrombomicroangiopathy and focal segmental glomerular sclerosis. The second subject was also biopsied for elevated creatinine (3.6 mg/dL, baseline 2.9 mg/dL) and ddcfDNA (6.4 %) and revealed C4d-positive chronic active anti-body mediated rejection (also shown on biopsy-two years prior). The third subject was biopsied for elevated creatinine (10.09 mg/dL, baseline 4.8 mg/dL) with a normal ddcfDNA (0.12 %) and revealed 90 % glomerulosclerosis consistent with recurrent diabetic nephropathy (Table 3).

3.4. Incidence of acute and chronic graft pathology in the pre-vaccine era

During the five year period prior to the availability of the first SARS-CoV-2 vaccine (January 2016 - December 2020), 107 eligible biopsies were performed on transplanted kidneys at our institution. During the same period, 352 transplants were performed, 16 of which (4.5 %) failed within the first year, giving 336 new transplanted kidneys with at least one year of function during the surveyed period. Of the 107 biopsies, chronic changes were present in 34.6 % (n = 37), acute changes in 72 % (n = 77), and both in 15 % (n = 16). Therefore, during the 5-year pre-vaccine period, the calculated incidences of biopsy-proven chronic and acute allograft pathologies were 11 % and 22.9 %, respectively.

4. Discussion

In this cohort of renal transplant recipients vaccinated against SARS-CoV-2, there was minimal evidence of donor-directed immunologic activity in the post-vaccination period with no cases of acute rejection. Increases and decreases in ddcfDNA levels were equally likely post-vaccination and were not correlated with changes in graft function as measured by serum creatinine. There were no cases of *de novo* DSA production; however, 5 % of subjects did experience increases in pre-existing DSA.

In the 5 % (n = 5) of subjects with elevations in DSA post-vaccination, two had biopsy-proven chronic graft dysfunctions in whom fluctuations in DSA are of unknown clinical significance. One had an associated elevated ddcfDNA (1.6 %) and had stable graft function greater than 10 years post-transplant; this subject was observed successfully. The remaining two subjects had low post-vaccine ddcfDNA levels, had stable graft function greater than 7 years post-transplant, and were observed successfully. We believe these data do not amount to evidence of post-vaccination donor-directed immune activation.

In the 10 % (n = 10) of subjects that experienced a 20 % increase in serum creatinine post-vaccination six had non-immunologic diag-

Table 2a
Depicts patient outcomes for subjects with > 20% change in DSA after second vaccination.[b]

Patients with Greater Than 20% Change in DSA [a]				
Patient	Cumulative MFI	% Change MFI	Biopsy[b]	Diagnosis/Intervention
A	17839	54%	Yes	Chronic Active AMR
B	5933	120%	Yes	Chronic TMA
C	27645	149%		
D	15121	869%		
E	30285	1252%		

[a]MFI = Mean fluorescence intensity, DSA = Donor Specific Antibodies
[b]Patient A and B required biopsies due to elevated creatinine and ddcfDNA.

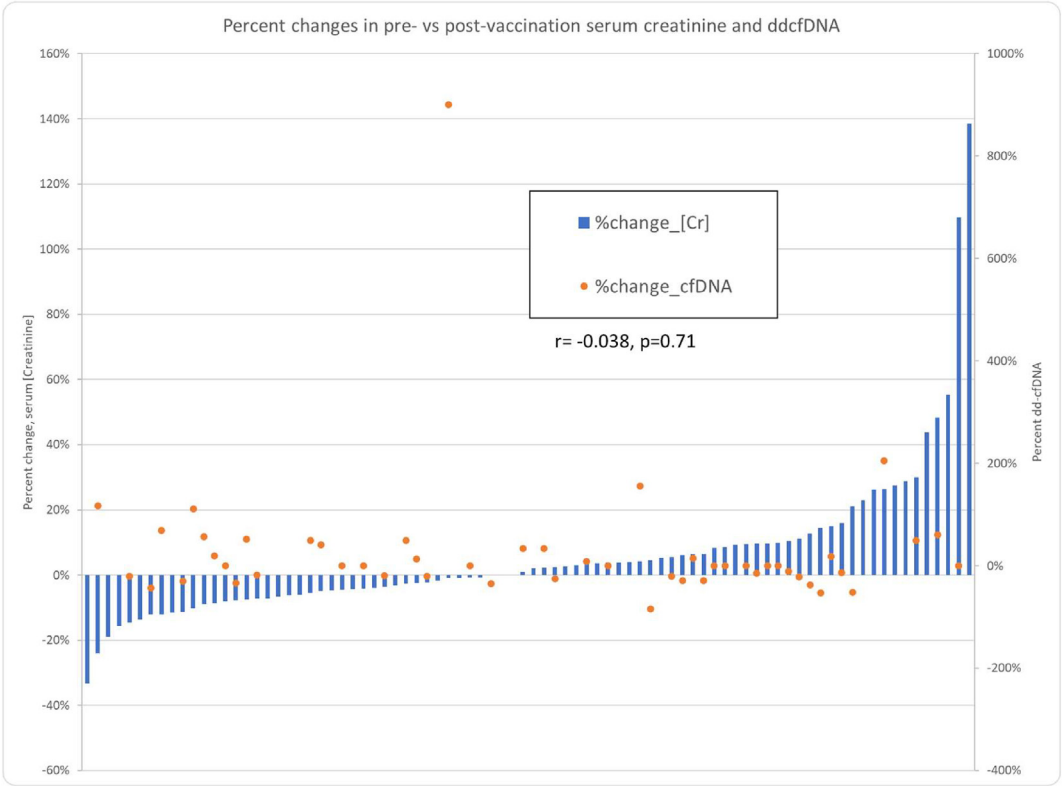

Fig. 1. Percent changes in pre- vs post-vaccination serum creatinine and ddcfDNA. *Abscissa: individual subjects. Left ordinate: percent change (post/pre) in serum creatinine concentration. Right ordinate: percent change (post/pre) in serum ddcfDNA.* Similar proportions of subjects experienced increases (n = 38, 39.6 %) and decreases (n = 43, 44.8 %) in serum creatinine in the post-vaccination period, p = 0.56. Similar proportions of subjects experienced increases (n = 22, 23 %) and decreases (n = 24, 25 %) in serum ddcfDNA in the post-vaccination period, p = 0.87. Pearson correlation: percent change in creatinine vs percent change in ddcfDNA (r = -0.031, p = 0.71).

Table 2b
Summary of Patients with DSA Greater Than 20%[a]

Table 2b summarizes the characteristics and overall % change in immunologic parameters for the 5.2% (n = 5) of patients with DSA MFI greater than 20% after second vaccination.

Patient Characteristics	n = 5
Age at vaccination, median age (IQR)	47.0 (13.15)
Female Gender, n (%)	1 (7)
Txp: vaccine, median years (IQR)	8.3 (6.1)
Vaccine[b], n (%)	
Moderna	1 (7)
Pfizer	4 (27)
J&J	0 (0)
Immunosuppression, n (%)	
Tacrolimus	3 (20)
Mycophenolate Mofetil	3 (20)
Prednisone	2 (13)
Belatacept	2 (13)
Results, median (IQR)	
% Change creatinine	37.32 (110)
% Change ddcfDNA	205 (840)
% Change DSA	149 (973.0)

[a]Txp: vaccine = Years from transplant to first vaccine dose, DSA = Donor-specific antibodies, IQR = Interquartile range
[b]All subjects received the same vaccine for both doses.

noses: three had biopsy-proven chronic graft dysfunctions, two had lower urinary tract infections, and one had new-onset atrial fibrillation. Although the remaining four had elevations from baseline without explanation, none were associated with an elevated ddcfDNA or had elevations to above 1.7 mg/dL. Although these subjects technically experienced an increase in serum creatinine, the changes were not clinically significant and were able to be managed with continued monitoring and optimization of maintenance immunosuppression.

Similarly, of the 16 % (n = 15) of subjects that experienced post-vaccination ddcfDNA levels of greater than 1 %, the two with associated elevations in creatinine had biopsy-proven chronic graft dysfunctions. The one subject with a markedly elevated ddcfDNA was within the first-year post-transplant and was recovering from a bout of treated acute cellular rejection (pre-vaccine ddcfDNA 12 %, post-vaccine ddcfDNA 5.7 %). The remainder showed stable graft function and was greater than a year-post transplant (median: 2.9 yrs.) and so no intervention was undertaken other than continued monitoring and optimization of maintenance immunosuppression.

This cohort of kidney transplant recipients vaccinated against SARS-CoV-2 was comprised of mostly long- and medium-term survivors with a median interval between transplantation and vaccination of 3.6 years. In a sub-analysis of the 20 % (n = 19) of subjects that were within the first-year post-transplant, there were no significant increases in serum creatinine [median percent change (IQR), −1% (12 %)] and only one subject with a post-vaccine ddcfDNA greater than 1 % (the aforementioned recovering acute rejection). Likewise, there were no increases in DSA in this group, largely owing to a lack of existing DSA pre-vaccination (only one subject had a single class II DSA). These data suggest that vaccination within the first-year post-transplant can still have a favorable donor-directed immunologic profile.

The generalization of the findings of this study are limited by the observational cohort design without a matched control group. We attempted to mitigate this limitation by providing institutional data from a five-year period prior to the availability of the SARS-CoV-2 vac-

Table 3a
depicts patient outcomes for those with a change in creatinine greater than 20% after second vaccination. [b]

Patients with Greater Than 20% Change in Creatinine [a]					
Patient	[Cr] 30 days post vaccine	% Change in [Cr]	ddcfDNA	Biopsy Performed	Intervention/Diagnosis
R	2.07	30.40%	0.12	No	
S	1.69	23.10%	0.18	No	
T	10.09	52.30%	0.12	Yes	90% Sclerosis (diabetes)
U	2.67	32.60%	0.96	No	
V	1.6	35.60%	0.83	No	
A	3.6	20.80%	6.4	Yes	Chronic AMR on prior biopsy
W	1.4	20.70%	0.38	No	
B	4.27	58.10%	1.2	Yes	Chronic TMA
X	0.88	21.60%	0.31	No	
Y	1.03	22.30%	0.33	No	

[a]ddcfDNA = donor-directed cell-free DNA, AMR = Antibody mediated rejection, TMA = Thrombotic Microangiopathy
[b]All subjects received the same vaccine for both doses

Table 3b
Summarizes patients with a change in creatinine greater than 20% after second vaccination. [a]

Summary of Patients with Change in Creatinine Greater Than 20%	
Patient Demographics	n = 10
Age at vaccination, median age (IQR)	56(15.08)
Female Gender, n (%)	7(58)
Txp: vaccine (yrs.)	6.43 (6.57)
Vaccine[b], n (%)	
Moderna	5(42)
Pfizer	7(58)
J&J	0(0)
Immunosuppression, n (%)	
Tacrolimus	8(67)
Mycophenolate Mofetil	11(92)
Prednisone	9(75)
Belatacept	3(25)
Results, median (IQR)	
% Change [Cr]	29(27)
ddcfDNA > 1%	3(25)

[a]Txp: vaccine = Years from transplant to first vaccine dose, DSA = Donor-specific antibodies, IQR = Interquartile range
[b]All subjects received the same vaccine for both doses

cine as a reference point. Indeed, compared to institutional rates of biopsy-proven chronic allograft pathology in the pre-vaccine era (11 %), the cohort of vaccinated patients with chronic pathologies on biopsy (3 %) compared favorably. Nonetheless, data from other populations may provide different results.

This cohort also represents an older subset of recipients with a median age of 56 years, skewed significantly toward older age. Only 13 % (n = 12) of subjects were younger than 40-years of age, a known high-immunologic risk group with respect to rejection. In this subset of subjects, there were no ddcfDNA > 1.0 % or DSA. One young patient (age 34 years) had a post-vaccination rise in creatinine of 26 % to a peak of 1.4 mg/dL; no intervention was undertaken other than continued monitoring and optimization of maintenance immunosuppression.

In summary, this cohort of renal transplant recipients vaccinated against SARS-CoV-2 demonstrated minimal evidence of donor-directed immunologic activity in the post-vaccination period. As this study was conducted early in the availability of SARS-CoV-2 vaccines, more investigation is likely needed with larger samples sizes into vaccine boosters, the optimal timing of vaccination post-transplant, and immunosuppression regimens in the peri-vaccination period. We believe these data to show that vaccination against SARS-CoV-2 is immunologically safe for renal transplant recipients and should continue to be aggressively pursued

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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