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TRANSPLANT INFECTIOUS DISEASE

LETTER TO THE EDITOR

Adverse events after SARS-CoV-2 vaccination in solid organ transplant recipients: A systematic review

To the Editor,

The immunogenicity in solid organ transplant (SOT) recipients against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination is suboptimal.[1] However, adverse events including rejection post-vaccination have not been reviewed, which are also of great interest for clinicians taking care of transplant recipients.

We conducted a systematic review on adverse events post SARS-CoV-2 vaccination in SOT recipients and included studies on SOT and SARS-CoV-2 vaccine safety including (a) systemic or local reactions, (b) organ rejection or de novo donor-specific antibodies (DSAs) (eFigure 1). We searched studies published between January 1, 2020 and August 11, 2021 through Medline, Embase, Scopus, Web of Science, CINAHL Plus with Full Text, LitCovid, medRxiv and bioRxiv. Records were downloaded to EndNoteX9, then uploaded to Covidence software for deduplication, screening, and extraction. We assessed studies' quality and bias using the Mixed Methods Appraisal Tool 2018 (eTable 1).

Through the search, we initially identified 74 unique articles. After review, we included 19 articles with 17 studies performing detailed safety assessments (Table 1). The most common side effect was injection-site pain, seen between 52.2% to 90% after vaccination. Fatigue, fever, myalgias, and arthralgias were also reported systemic reactions. Local reactions included pain, erythema, and swelling.

We identified two case reports and three cohort studies reporting organ rejection after vaccination, including one kidney, one liver, one heart transplant recipient, and two nonspecified SOT recipients (Table 2). For three cohort studies, of 1721 recipients, three recipients developed rejection.[3,4] Acute cell-mediated rejection was seen at 8- and 11-days post-vaccination in the kidney[2] and liver transplant recipient,[5] respectively. No documented graft failure was reported. Three/four studies did not identify any de novo or increase in DSA after screening before and within 1–3 weeks of mRNA vaccine doses (Table 1).[2–4] One/thirteen kidney transplant recipients developed donor-specific anti-HLA class II antibody 28 days after the second dose of BNT162b2 vaccine which increased after the third dose, without allograft rejection.[5]

Our study found a very limited number of cases of organ rejection or significant side effects in SOT recipients after SARS-CoV-2 vaccination. The vaccine immunogenicity is still suboptimal in this population.[1] On top of this, breakthrough infections have been widely reported. However, SARS-CoV-2 vaccination has a relatively safe profile in SOT recipients, and thus vaccination of this population can be justified. SOT recipients should still maintain all precautions to prevent infection, such as frequent hand washing, masking, and use of pre-exposure monoclonal antibodies.

There are several limitations in this study. We found a lack of high-quality, controlled studies evaluating rejection episodes after SARS-CoV-2 vaccination, with all published studies being case reports or series. Thus, there could be publication and reporting bias. Furthermore, long-term outcomes were not assessed even in large prospective studies, given the recency of SARS-CoV-2 vaccinations.

In conclusion, even though SARS-CoV-2 vaccine immunogenicity is suboptimal in SOT recipients, given the safety profile, we recommend providing vaccination to SOT recipients in addition to other preventive strategies. Long-term follow-up studies on outcomes including rejection post-SARS-CoV-2 vaccination are warranted in SOT recipients.

Abbreviations: DSA, donor-specific antibodies; SARS-CoV-2, Severe acute respiratory virus syndrome 2; SOT, solid organ transplant.

TABLE 1 Studies reporting safety of SARS-CoV-2 vaccination in solid organ (SOT) transplant recipients[a]

First author and year	Study design	SOT patients (*N*)	Vaccine type and schedule	Follow-up	Local reactions	Systemic reactions	Most common AE	Donor-specific antibodies monitoring[b]
Boyarsky 2021	Cross-sectional survey	187	mRNA (BNT162b2 or mRNA-1273), one dose	1 week post-dose 1	Pain Erythema Swelling	Fever Chills Fatigue Headache Vomiting Diarrhea Myalgias	Injection-site pain (90%)	NR
Cucchiari 2021	Prospective cohort	148	mRNA-1273), two doses	48–72 h after each dose	Pain Erythema Swelling	Fever Fatigue Chills Nausea or vomiting Diarrhea Myalgia Arthralgias Headache	Injection-site pain (86% post dose 1, 75% post dose 2) Fatigue (25% post dose 1, 27% post dose 2)	DSA tested at baseline and 2 weeks post dose 2: present in five cases at baseline (3.4% of the entire population); no cases of de-novo DSAs observed after dose 2 of mRNA-1273
Grupper 2021[c]	Retrospective cohort	136	BNT162b2, two doses	7 days after each dose	Pain Erythema Swelling Regional lymphadenopathy	Fever Chills Headache Fatigue, Myalgia Arthralgia Nausea Vomiting Diarrhea	Injection-site pain (52.2%)	NR
Hall 2021a	Prospective cohort	127	mRNA-1273 vaccine, two doses ($n = 126$ patients) mRNA-1273 vaccine, one dose ($n = 1$)	Vaccine diary for 7 days after each dose, overall follow-up > = 60 days post-dose 1	Pain Erythema Swelling	Fatigue Myalgia Headache Arthralgia Nausea or vomiting Chills Medical visit	Injection-site pain (>60% post dose 1, >20% post dose 2)	NR
Hall 2021b	Randomized controlled trial	60	mRNA-1273, three doses (treatment group)	Vaccine diary for 7 days after each injection, overall follow-up > = 4 weeks post-dose 3	Pain Swelling	Fever Chills Fatigue Myalgia Arthralgia Headache Nausea or vomiting Diarrhea	Injection-site pain (46/60, 76.7%) post dose 3	NR

(Continues)

TABLE 1 (Continued)

First author and year	Study design	SOT patients (*N*)	Vaccine type and schedule	Follow-up	Local reactions	Systemic reactions	Most common AE	Donor-specific antibodies monitoring[b]
Herrera 2021	Prospective cohort	104	mRNA-1273, two doses	48–72 h after each dose	Pain Swelling	Fatigue, fever	Injection-site pain (80%)	No increase in HLA antibodies from baseline to 3 weeks post dose 2
Itzhaki Ben Zadok 2021	Prospective cohort	42	BNT162b2, two doses	Days 21–26 and 35–40 post-dose 1	Pain Erythema	Fatigue Myalgia Arthralgia Headache Fever	Injection-site pain (71%)	NR
Kamar 2021	Retrospective cohort	101	BNT162b2, three doses	1 month post-dose 3	NR	NR	NR	NR
Marion 2021	Retrospective cohort	950	mRNA (BNT162b2 or mRNA-1273), two doses	4 weeks post-dose 2	NR	NR	NR	NR
Massa 2021	Prospective cohort	61	BNT162b2, three doses	72 h after each dose	Injection-site pain Local paresthesia	Fatigue Headache Diarrhea Fever Myalgia Rhinorrhea Nausea and vomiting Cough Hypertension Anorexia Vertigo Abdominal pain Insomnia	Injection-site pain in 60.7%, 65.6%, and 67.2% (41 of 61 patients) after dose 1, 2, and 3, respectively	Thirteen (21.3%) patients had donor-specific antibodies before vaccination. Only one patient developed de novo donor-specific antibodies, donor-specific anti-HLA class II (DQB1*06:03) antibody 28 days after the second vaccine dose
Mazzola 2021	Retrospective cohort	143	BNT162b2, two doses	7 days post-dose 1, up to 1 month post-dose 2	Pain	Fatigue headache	Injection-site pain (25.7%)	NR
Ou 2021a	Prospective cohort	609	BNT162b2, two doses	7 days after each dose	Pain Swelling Erythema	Fatigue Headache Myalgias Chills Fever Diarrhea Vomiting	Injection-site pain after dose 1 (24% in the non-belatacept group, 22% in the belatacept group). Fatigue after dose 2 (21% in the non-belatacept group, 17% in the belatacept group)	NR

(Continues)

TABLE 1 (Continued)

First author and year	Study design	SOT patients (N)	Vaccine type and schedule	Follow-up	Local reactions	Systemic reactions	Most common AE	Donor-specific antibodies monitoring[b]
Ou 2021b	Prospective cohort	741	BNT162b2, two doses (n = 400) mRNA-1273 vaccination, 2 doses (n-341)	7 days after each dose	Pain Swelling Erythema	Fatigue Headache Myalgia Chills Fever Diarrhea Vomiting	Injection-site pain (84% after dose 1, 77% after dose 2)	NR
Peled 2021	Prospective cohort	77	BNT162b2, two doses	7 days after each dose	Pain Erythema Swelling	Fatigue Headache Chills Vomiting Diarrhea New or worsening muscle or joint pain Use of antipyretic or pain medication	Injection-site pain in 56% and 49% after dose 1 and 2, respectively	NR
Rabinowich 2021	Case-control	Liver (n = 71) Controls (n = 21)	BNT162b2, two doses	Survey 7 days post each dose, follow up until 7–10 weeks post-dose 2	Pain	Fatigue headache myalgias	Injection-site pain in each group following the dose 1 and 2: 43/71, 60.5% (LTR) versus 15/21, 71% (controls); 38/71, 53.5% (LTR) versus 15/21, 71% (controls); respectively	NR
Shostak 2021	Prospective cohort	168	BNT162b2, two doses	Median of 68 days (IQR 65–73) post-dose 1	Pain	Fatigue	Injection-site pain (108/168, 64.29%)	NR
Werbel 2021	Case series	30	Three-dose schedule Initial: BNT162b2, 2 doses (*n* = 17); mRNA-1273, 2 doses (*n* = 13) Dose 3: JNJ-78436735 (*n* = 15), mRNA-1273 (*n* = 9), BNT162b2 (*n* = 6)	Survey 7 days post-dose 3, follow-up limited	Pain Erythema Swelling	Chills Headache Fatigue Myalgia Diarrhea	Fatigue in 8/11 (72.73%) of J&J recipients Injection-site pain in 12/12 (100%) of mRNA recipients	NR

Abbreviations: AE, adverse event; NR, not reported; URI, upper respiratory infection; UTI, urinary tract infection.

[a] References for the table can be found on the Supplement.

[b] The study by Sattler et al.[4] also monitored HLA-specific antibodies with no increase from baseline seen; however no detailed safety assessment was performed.

[c] One patient with undetectable antibody levels despite full vaccination died from severe PCR-proven COVID-19.

TABLE 2 Studies reporting transplant rejection following vaccination in solid organ transplant (SOT) recipients[a]

Author and year	Patient (type of organ transplant)	Vaccine and schedule	Time from transplant	Time from last vaccine dose to diagnosis	Case	Findings
Del Bello 2021	Kidney	BNT162b2, two doses	18 months	8 days	Biopsy-proven acute cellular rejection	Detectable donor-specific antihuman leukocyte antigen antibodies (DSAs) against class II antigens, and anti-SARS-CoV-2 spike protein antibodies. Later kidney function improved with steroid pulses
Marion 2021	SOT (not specified)	mRNA	NR	NR	Acute cellular rejection	No biological monitoring
Ou 2021b	SOT (not specified)	mRNA, two doses	NR	NR	Acute rejection	-
Vyhmeister 2021	Liver	mRNA-1273 vaccine, one dose	5.5 months	11 days	Biopsy-proven acute cellular rejection	Presented with newly elevated liver tests, dark urine, fatigue and malaise. Underwent three liver biopsies due to nonresponse to steroids, later improved with antithymocyte globulin. DSA antibodies were negative, antibodies to the antispike protein S1 subunit were present but not to the receptor binding domain.
Werbel 2021	Heart	mRNA-1273 vaccine following 2 BNT162b2 doses	NR	7 days	Biopsy-proven, antibody-mediated rejection	Presented with volume overload, heart function preserved

Abbreviation: NR, not reported.
[a]References for the table can be found on the Supplement.

AUTHOR CONTRIBUTIONS

AV, YE, and JMR performed the literature search. All authors were responsible for the study design, data interpretation, and writing of the manuscript and are accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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