EDITORIAL

COVID-19 vaccination immune paresis in heart and lung transplantation

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Vaccines against symptomatic coronavirus disease-19 (COVID-19) demonstrate marked efficacy within clinical trials of immunocompetent persons with significant reduction in severe COVID-19 disease, hospitalization and death.[1−3] These vaccines utilize mRNA, replication-deficient adenovirus vectors, inactivated SARS-CoV-2 virus, or protein subunits of SARS-CoV-2.[4] Most vaccines target the viral spike protein and the receptor-binding domain (RBD) which facilitates viral entry, and are designed to stimulate both cellular (T-regulatory and T-helper cells) and humoral (IgG anti spike and/or anti-RBD antibody) immune responses.[5] Animal studies have indicated protection with cellular response, even when antibody titers are sub-optimal.[6] Thus, while serological attributes to vaccination are surrogates for immune reactogenicity, their specific correlation with clinical efficacy remains uncertain.

Since immunosuppressed recipients of solid organ transplantation (SOT) are at increased risk of poor outcome following COVID-19 illness, most organizations, including the *International Society of Heart and Lung Transplantation*, have promoted COVID-19 vaccination in this population despite uncertainty of vaccine responses and clinical efficacy.[7,8] Evidence of vaccine-based immune responses in transplant recipients is emerging. Boyarsky and colleagues assessed the immune response to the 2nd dose of either mRNA vaccines (Pfizer-BioNTech and Moderna) in 658 SOT recipients.[9] Anti-spike protein antibodies were detected in 54% of participants at a median of 29 days from the second vaccine dose in stark contrast to higher rates noted in the general population. Of 97 heart transplant (HT) recipients 57% had detectable IgG while the 71-lung transplant (LT) recipients elucidated IgG antibodies in only 39%. Use of antimetabolites (such as mycophenolic acid) was associated with poor response. Other studies in kidney transplantation have also confirmed a sub-optimal antibody response.[10−13] One study assessed T-cell responses and noted that most transplanted patients mounted spike-specific T helper cell responses, albeit in significantly reduced frequency compared to controls and dialysis patients.[12]

Two separate studies in the *Journal* in heart (Peled et al) or lung (Havlin et al) transplantation shed light on post vaccination immune responses in this specific population after two doses of vaccine.[14,15] Peled et al report on 77 HT recipients who received the Pfizer-BioNTech vaccine and noted presence of anti-spike IgG antibodies in only 18% of patients at 3 weeks following the second dose. Neutralizing antibody titers were found in just half of those with detectable antibody responses.[14] In the LT study of 48 patients, Havlin and colleagues were unable to demonstrate any

Table 1 Summary of clinical studies assessing the immune response to mRNA vaccinations in the setting of solid organ transplantation.

Publication	Study population	Vaccine, dose	Outcome	Results, comments
Boyarsky et al[9]	658 SOT recipients	Pfizer-BioNTech and Moderna, one dose	[a]Antibody response	357/658 (54%) with detectable IgG at median 29 days after Dose 2. Older age, use of mycophenolate, use of Pfizer BioNTech vaccine and time since transplant was associated with negative serology.
Yi et al[10]	145 KT recipients	Pfizer-BioNTech and Moderna, one dose	Antibody response (unknown test)	8/145 (5.5%) with anti-spike IgG measured prior to Dose 2. No additional data re: timing from vaccine dose, risk factors.
Benotmane et al[11]	242 KT recipients	Moderna, one dose	[a]Antibody response	26/242 (10.7%) with detectable anti-spike IgG at 28 days from Dose 1. Shorter time from transplant and use of anti-thymocyte globulin, mycophenolate and steroids associated with negative serology by univariate analysis.
Grupper et al.[13]	136 KT recipients	Pfizer BioNTech, two doses	Antibody response	51/136 (37.5%) with detectable IgG at median 16 days after Dose 2. Negative serology associated with increasing age, pre-transplant dialysis duration, living donor, high dose steroids in previous 12 months, mycophenolate, triple immunosuppression, low lymphocyte count, higher serum creatinine and lower GFR by univariate analysis
Sattler et al[12]	39 KT recipients	Pfizer BioNTech, two doses	[a]Antibody and T-cell response	1/39 (2.6%) had IgG seroconversion at 8 days following Dose 2. Prevalence of spike specific CD4 cells was similar to controls 36/39 (92%), spike specific CD8 cell response only noted in 2/29 (5.13%) No alloreactivity noted.
Peled et al[14]	77 HT recipients	Pfizer BioNTech, two doses	[a]Antibody response	14/77 (18%) with detectable RBD IgG at mean 21 days following Dose 2. Mycophenolate use associated with lower odds of seroconversion in multivariate analysis. No serious adverse events noted by 41 days from Dose 2.
Havlin et al[15]	48 LT recipients	Pfizer BioNTech, two doses		

Table 1 (*Continued*)

Publication	Study population	Vaccine, dose	Outcome	Results, comments
			[a]Antibody and T-cell response	0/30 patients had detectable RBD IgG at one week following Dose 2 and 0/21 at 4-6 weeks following Dose 2. SARS-CoV-2 specific T-cells noted in 4/12 (33.3%) 9 weeks after Dose 2. Mycophenolate use associated with lack of IgG in univariate analysis.

SOT is solid organ transplant, KT is kidney transplant, HT is heart transplant, LT is lung transplant.

[a]Antibody testing for SARS-CoV-2 anti-spike IgG was performed by the following tests: *Boyarsky et al* - anti-SARS-CoV-2 Spike S1 IgG ELISA (Euroimmun, Lubeck, Germany). Some samples tested using the SARS-CoV-2 S enzyme immunoassay (Roche Elecsys) that tests for antibodies against the receptor-binding domain of the SARS-CoV-2 spike protein.

Yi et al — not mentioned in paper.

Benotmane et al - ARCHITECT IgG II Quant test (Abbott, Abbott Park, IL). Titer > 50 arbitrary units (AUs)/ml considered positive.

Grupper et al - LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescent assay (DiaSorin S.p.A., Saluggia, Italy) used to detect IgG antibodies directed against a recombinant S protein (S1/S2). Titers ≥15 AU/mL considered positive.

Sattler et al — Anti-SARS-CoV2 spike S1 domain-specific IgG ELISA (Euroimmun, Lübeck, Germany). OD ratios of ≥1.1 considered positive.

Peled et al - In-house ELISA that detects IgG against SARS-CoV-2 RBD.

Havlin et al - anti-SARS-CoV-2 Spike S1 IgG ELISA (Euroimmun, Lubeck, Germany) and confirmed independently by Microblot-Array COVID-19 IgG against a mix of recombinant antigens (TestLine Clinical Diagnostics, Brno, Czech Republic) and chemiluminiscent immunoassay (CLIA) Liaison SARS-CoV-2 Trimeric S IgG against the trimeric spike S1 protein (Diasorin, Saluggia, Italy).

antibody response at 4 to 6 weeks after the second dose of the Pfizer-BioNTech vaccine. The LT study also tested T-cell responses in a subgroup of 12 patients and noted such responses in a third of tested patients. Intriguingly, Havlin et al compared their findings to 33 LT recipients who acquired COVID-19 illness and demonstrated that 85% of these patients had anti-spike IgG within 3 months of SARS-CoV-2 infection.[15]

These observations of immune paresis (defined as a weaker humoral and cellular response than expected to an antigenic stimulus) in heart or lung transplant recipients are not unique to the COVID-19 vaccine in SOT recipients, since lower rates of immune response have been reported with other vaccines.[16] The variable antibody response seen in recent studies (Table 1) may reflect differences in serological assay sensitivities.[9, 10–13] Additionally, the timing of assessment may be in play since following COVID-19 illness, peak IgG responses in otherwise healthy individuals appear at 4 to 5 weeks.[17,18] Longitudinal studies also indicate a delayed IgG seroconversion and lower IgG titers when immunosuppressed individuals suffer COVID-19 illness.[19] It is intriguing that Havlin et al noted a more robust immune response in patients after COVID-19 infection in contrast to the minimal response following vaccination. Perhaps transplant recipients require a higher antigen load as achieved in natural infection or this may reflect better immune response in the setting of reducing immunosuppression during the infection phase of illness. Thus, the observed reduced serological response in the setting of vaccination suggest that immune paresis, perhaps promoted by use of antimetabolite therapy is the most likely explanation. A report of COVID-19 illness events in 7 vaccinated transplant recipients (5 with two full doses) at a median of 28 days following last dose of vaccine did not show

detectable anti-spike antibodies at presentation and in most cases required treatment in the hospital.[20]

Observations from vaccine responses for diseases other than COVID-19 in immunosuppressed individuals may provide insight into further clinical studies. Studies of influenza vaccination in SOT demonstrate greater seroconversion rates and higher antibody titers in high dose influenza vaccines compared with a standard dose.[21,22] Use of an in-season influenza vaccine booster is associated with greater seroconversion in SOT recipients.[23] Such observations point to a need to adequately study initial antigenic dose, duration post-dose when adequate serological responses occur and need for an additional booster dose in the context of COVID-19 vaccination. Importantly, clinically relevant outcomes of disease severity, healthcare resource source and death need to be assessed for SOT vaccines.

The finding of an association of immune paresis with use of antimetabolites such as mycophenolate mofetil deserves discussion. Such correlations must not be assumed to indicate that the drug should be stopped in order to facilitate a better vaccine response. Withdrawal of antimetabolite therapy may predispose to development of donor specific antibodies, promote the possibility of antibody mediated rejection or cellular rejection of the allograft, and promote possibility for chronic allograft complications and late loss. Therefore, such clinical actions should only be carried out in well controlled studies under conditions of close surveillance.

In the absence of effective vaccination strategies, consideration may be directed to prophylactic administration of monoclonal antibodies in selected heavily immunosuppressed patients who experience a household exposure, in a manner similar to strategies underway in vulnerable populations such as nursing home residents.[24,25] We must

advocate for vaccine priority of household members of transplant recipients in order to reduce the risk of infection exposure. It is imperative that transplant candidates be vaccinated while wait-listed since their immune responses are likely to be better prior to receiving the organ. The low immune responses in immunosuppressed individuals suggest that they must not let their guard down once vaccinated and should continue to practice optimal hygiene, masking and maintain social distancing.

Despite the observation of immune paresis in SOT, we emphasize that much remains unknown with respect to the timing of achieving an adequate immune response, optimal serological corelates that confer clinical immunity, assessment of T-cell response, and importantly, lack of clinical outcomes data after COVID-19 vaccination in SOT recipients. Due to these ongoing gaps in our understanding, we continue to endorse COVID-19 vaccination in our transplant recipients, without alteration in immunosuppressive regimens, given a low risk of serious adverse events and the greater potential for clinical benefit.

Conflict of Interest

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