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Editorial Article

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Pre-Solid-Organ-Transplant COVID-19 Vaccination

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Vaccine such as influenza vaccine, is administered in stable transplant recipients, although live attenuated virus vaccines are contraindicated, generally due to risk of disseminated infection [1, 2]. Neither efficacy, safety, nor durability are well known in transplant recipients due to exclusion of them from recent COVID-19 vaccine trials [1, 2]. Currently, there are no SARS-CoV-2 vaccine platforms using attenuated live virus approved in phase III trials. Nevertheless, if they are approved for use, concerns, including potential decrease in efficacy in immunocompromised patients, potential for vaccine-related allograft rejection, unknown durability of the immune response, and long-term safety data still exist. Due to experience with neither the influenza vaccine nor the adjuvant recombinant zoster vaccine having been related to allograft rejection, successful administration of influenza and adjuvanted recombinant zoster vaccines to stable transplant recipients, and unanticipated vaccine-related adverse events to the allograft having not borne out, the influenza and adjuvanted recombinant zoster vaccines are able to be extrapolated to COVID-19 vaccines [2, 3]. In immunocompromised host, concerns for adenoviral vector vaccines are focused on a viral infection, but these concerns have no scientific evidence. Although newly approved adenoviral-vector use for vaccination, this vaccine platform has been used for decades for gene therapy for cancer and other rare diseases. Inactivated virus and protein subunit vaccine platforms that have been used in transplant recipients for other infections, such as human papilloma virus, pertussis, and hepatitis A and B, are currently under investigation for SARS-CoV-2 (COVID-19) infection in transplant recipients [2].

A previous prospective cohort study in the US, approved by the Johns Hopkins University institutional review board was conducted among 436 transplant recipients (median age 55.9 years (IQR : 41.3-67.4 years), 61 % of women, 89 % of White transplant recipients, 52 % received the BNT162b2 (Pfizer/BioNTech) and 48 % received the mRNA-1273 vaccine (Moderna), median time since transplant of 6.2 years (IQR : 2.7-12.7 years, maintenance immunosuppression regimen : tacrolimus (83 %), corticosteroids (54 %), mycophenolate (66 %), azathioprine (9 %), sirolimus (4 %), and everolimus (2 %)), who underwent COVID-19 vaccination between 16, 2020 and February 5, 2021. The participants underwent either standard venipuncture or at-home blood sampling with the TAPII blood collection device (Seventh Sense Biosystems), tested for antibodies to the S1 domain of the SARS-CoV-2 spike protein by using an enzyme immunoassay (EUROIMMUN), whereas the venipuncture samples were tested for antibodies against the receptor-binding domain of the SARS-CoV-2 spike protein by using the anti-SARS-CoV-2 enzyme immunoassay (Roche Elecsys) [4, 5]. Both EUROIMMUN (sensitivity of 87.1 %, specificity of 98.9 %) and Roche Elecsys (sensitivity of 84.0 %, specificity of 100 %) tests are semiquantitative, consistently correlated with neutralizing immunity, and correspond to mRNA vaccine antigens [6-8].

The antispike antibody assays used during immunogenicity assessments in mRNA vaccine clinical trials are analogous to these two assays [4]. The study revealed that after the first dose of COVID-19 vaccine at a median of 20 days (IQR : 17-24 days), 76 of 436 participants (17 %, 95 % CI : 14 %-21 %) demonstrated detectable antibody (anti-S1 or anti-receptor-binding domain, 31 in 41 kidney transplant recipients, 28 in 37 liver transplant recipients, 9 in 12 heart transplant recipients, 4 in 5 lung transplant recipients, 1 in 1 pancreas transplant recipient, 2 in 3 multiorgan transplant recipients) [4]. Those participants who received mRNA-1273 vaccine (Moderna) were more likely to develop an antibody response than those receiving BNT162b2 vaccine (Pfizer/BioNTech) (69 % vs 31 %, respectively; adjusted incidence rate ratio (IRR) : 2.15 (95 % CI : 1.29-3.57); p = 0.003) (This association was similar in a sentivity analysis limited to those tested 14 to 21 days after vaccination (n = 245; adjusted IRR : 2.29 (95 % CI : 1.32-3.94); p = 0.003) [4]. Older transplant recipients were less likely to develop an antibody response (adjusted IRR : 0.83 (95 % CI : 0.73-0.93) per 10 years; p = 0.002) [4]. Nevertheless, younger transplant recipients not receiving anti-metabolite maintenance immunosuppression and those younger transplant recipients receiving the mRNA-1273 vaccine (Moderna) were more likely to develop

antibody responses [4]. Transplant recipients who receiving anti-metabolite maintenance immunosuppression therapy were less likely to develop an antibody response than those participants not receiving immunosuppression therapy (37 % vs 63 %, respective; adjusted IRR : 0.22 (95 % CI: 0.15-0.34); $p < 0.001$) that contrast with the early immunogenicity identified in mRNA vaccine trials [4]. These results also include 100 % antispike seroconversion by the day 15 after mRNA-1273 (Moderna) and the day 21 after BNT162b2 (Pfizer/BioNTech) vaccination that contrast with the early immunogenicity identified in mRNA vaccine trials [4, 9, 10]. Poor antispike antibody responses in transplant recipients after first dose of mRNA vaccination indicate that despite COVID-19 vaccination, such organ transplant recipients may still be at higher early risk for COVID-19 infection. Characterization of memory B-cell and T-cell responses and advanced immunophenotyping of transplant recipients after COVID-19 vaccination will be significant in determining immunological responses and vaccination strategies after the second dose of COVID-19 vaccine.

As of December 31, 2020, when focusing on kidney transplant recipients, there is no evidence of mRNA-vaccine-platform (BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna))-induced off-target immune responses in large phase III clinical trials, no replicative potential through homologous recombination demonstrated in AdV-vectored vaccine platform (AZD1222 (Oxford/AstraZeneca), JNJ78436735/Ad26.COV2.S (Janssen), Convidecia (Ad5-nCoV), Sputnik V (Gamaleya)), does not contain live virus in protein subunit vaccine platform (NVX-CoV2373 (Novavax), SARS-CoV-2 recombinant protein formulation (GSK/Sanofi) (Matrix-M1 contains the same QS21 saponin as the AS01 B adjuvant system contained in the recombinant varicella zoster vaccine) and no association between AS03 exposure and graft rejection (high incidence of anti-HLA antibodies in KTR vaccinated with AS03-adjuvanted influenza vaccines) in protein subunit vaccine platform, and does not contain live virus and limited data available in peer-reviewed literature in whole-inactivated (killed) vaccine platform (EpiVacCorona (Vector Institute), BBIBP-CoV (Sinopharm), CoronaVac (SinoVac) [11-16]. Several transplant organizations, such as American Society of Transplantation, The International Society for Heart and Lung Transplantation, American Association for the Study of Liver Diseases, American Society of Transplant Surgeons, International Transplant Nurses Society, The Transplantation Society, NATCO, UNOS, Leading the Way in Organ Transplantation, Canadian Society of Transplantation, Pediatric Infectious Diseases Society, Association of Organ Procurement Organizations, American Society for Histocompatibility and Immunogenetics, International Liver Transplantation Society, The Alliance, Transplant Infectious Disease, International Pediatric Transplant Association, and International Society of Vascularized Composite Allotransplantation established their statement on COVID-19 vaccination in solid-organ transplant (SOT) recipients as the following : 1) Pre-transplant vaccination of all SOT candidates as a priority whenever feasible, 2) Continued SARS-CoV-2 (COVID-19) vaccination in SOT recipients and priority for vaccination of their household members and caregivers to decrease exposure risk for these vulnerable patients, 3) Continuation of a stable immunosuppression regimen at the time of vaccination to avoid the risk of organ rejection until more comprehensive data are available, and 4) Continued adherence of all transplant recipients to protect measures, including facial masking and social distancing regardless of vaccination status [17].

In conclusion, despite many weeks of suitable medical care in COVID-19 patients with advanced disease severity, consideration of lung transplantation may be limited to them. Further studies are urgently needed to identify COVID-19 patients with progression of irreversible lung damage who might take benefit from early lung transplantation.

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