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EDITORIAL COMMENT

Efficacy of the COVID-19 vaccine in heart transplant recipients: what we know and what we ignore

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This article refers to 'Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients – a prospective cohort study' by O. Itzhaki Ben Zadok *et al.*, published in this issue on pages 1555–1559.

Infectious diseases are a well-known major complication after solid organ transplantation. Heart transplant (HT) patients have a high mortality rate after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with figures of up to 25% reported.[1] Vaccines to prevent coronavirus disease 2019 (COVID-19) have shown efficacy in generating specific immune response to virus antigens and neutralizing antibodies, as well as clinical efficacy in reducing the risk and severity of symptomatic disease.[2–5] However, efficacy in the HT population is not well known, as solid organ transplant patients were excluded from clinical trials of SARS-CoV-2 mRNA vaccines. A recent study evaluated in 436 solid organ recipients the immune response to the first dose of an mRNA vaccine (BNT162b2, Pfizer-BioNTech, or mRNA-1273, Moderna)[6] and found anti-Spike IgG antibodies in only 17% of participants after a median follow-up of 20 days. Of the 66 patients with HT, antibodies were detected in only 14%. Older age and treatment with antimetabolites were associated with a lower immune response. Also, the frequency of immune response was higher after mRNA1273 vaccine compared to BNT162b2 vaccine (69% vs. 31%, $P = 0.003$).[6] Studies in kidney[7,8] and liver[9] transplant patients confirm this low post-vaccine mRNA SARS-CoV-2 immune response.

In this issue of the Journal, Itzhaki Ben Zadok *et al.*[10] report, in a prospective single-centre study in Israel, the short-term immunogenicity response following vaccination for SARS-CoV-2 with the two-dose mRNA vaccine BNT162b2, Pfizer BioNTech, in a population of 42 HT patients. Anti-spike IgG (S-IgG) antibodies were determined at two pre-specified time points; between days 21 to 26 and between 35 to 40 days after the first dose of vaccine and S-IgG value of ≥50 AU/mL or higher was considered positive. The study population was analysed in three subgroups to better characterize post-vaccine immunogenicity: Group I, seropositive antibody response after the first dose of vaccine; Group II, seropositive antibody response after either the first or second dose; and Group III, seroconversion after the second dose in non-responders to the first dose.

The percentage of patients with seropositivity for S-IgG antibodies was 15%, 49% and 32% in groups I, II and III, respectively. Analysing the baseline characteristics of the patients, according to whether they had serologic response to the two doses of the vaccine (responders, $n = 18$) or not (non-responders, $n = 19$), older patients and those with immunosuppression protocols that included antimetabolites [mycophenolate mofetil (MMF), mycophenolic acid] were associated with lower immune response. Median age (25th–75th quartiles) in responders vs. non-responders was 46 years (34–63) vs. 68 years (59–70), respectively ($P = 0.03$). The percentage of antimetabolite-based immunosuppression protocols was 44% in responders vs. 89% in non-responders ($P = 0.011$).

The efficacy of the vaccines considering COVID-19 as the main outcome was around 95% for mRNA vaccines and 70% for adenovirus vector vaccines, and efficacy against severe disease was close to 100%.[2,3]

The serological response to vaccines, in general, in the solid organ transplant population is poor and, furthermore, knowledge is limited and recommendations remain poorly supported by scientific evidence, due to the absence of well-defined clinical trials in this population. In a systematic review, it was observed that response varies with vaccine type, age and organ transplanted and in some vaccines the antibody titre decreases rapidly.[11] Regarding COVID-19 vaccines, as with other vaccines in the transplant population, it is important to know the efficacy in preventing the disease

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and at the same time the safety in terms of adverse reactions to the vaccine or risk of rejection.

Transplant recipients were excluded from the large clinical trials of COVID-19 vaccines so efficacy, durability and safety data in these patients are unknown. Studies of immune response following COVID-19 vaccination in solid organ transplants have been heterogeneous, both in terms of timing of post-vaccine assessment and type of response (humoral and/or T-cell), although most have focused on assessing antibody titre. Therefore, any study that measures the post-vaccination COVID-19 immune response and add knowledge is welcome.

This low serological response has been seen in other solid-organ transplantation studies and with other types of mRNA vaccines. In another prospective study, also from Israel,[12] in HT patients vaccinated with two doses of the BNT162b2 vaccine, anti-receptor-binding domain IgG antibodies, after an average of 21 days after the second dose, were detected in only 18% of patients. The immunosuppressive regimen containing MMF was also associated with a lower antibody response rate. At a median follow-up of 41 days after the second dose, there were no clinical episodes of rejection, suggested by troponin leak or graft dysfunction. A study in 80 liver transplant recipients from Israel, vaccinated with two doses of BNT162b2 vaccine, the antibody response was 47.5% vs. 100% in 25 healthy controls ($P < 0.001$). Antibody titre was also significantly lower in this group (mean 95.41 AU/mL vs. 200.5 AU/mL in controls, $P < 0.001$). Older age, lower estimated glomerular filtration rate and immunosuppression medications (use of high-dose prednisone in the past 12 months, MMF and triple therapy immunosuppression) were associated with lower antibody response.[9] A study in 205 kidney transplant recipients vaccinated with two doses of mRNA-1273 SARS-CoV-2 vaccine showed a serological response 28 days after the second dose in 48% of patients.[8]

Due to the weak response after two doses of vaccine in solid organ transplant recipients, the possibility of a third dose has been suggested, and a recent French study explored the humoral response following this strategy with the BNT162b2 vaccine.[13] The study included 101 transplant recipients (78 renal, 12 hepatic, 8 pulmonary or cardiac, and 3 pancreatic) who were given the first two doses of vaccine spaced 1 month apart and the third dose about 2 months after the second dose. Antibody response was assessed before each dose and 4 weeks after the third dose. The prevalence of anti-SARS-CoV-2 antibodies before and after the third dose increased from 40% to 68%. Among those patients who were seronegative before the third dose, 44% were positive after the third dose and, among those patients seropositive before the third dose, all remained positive and the antibody titre increased from 32 ± 12 to 2676 ± 350 ($P < 0.001$). No serious adverse effects or rejection were reported, although follow-up was short.

A recent joint AST/ISHLT/ASTS statement, taking into account all the doubts and concerns that are arising in relation to studies showing a low rate of serological response to COVID-19 vaccines in transplant recipients, and on the basis that the scientific evidence is not sufficient to draw firm conclusions, and given that vaccination is critical to contain the spread of the pandemic, makes some advice on what we are learning about efficacy in organ transplant recipients. The statement strongly recommends that all solid organ transplant recipients should be vaccinated against SARS-CoV-2 to minimize risks using local approved vaccines and that booster doses are used in the context of clinical research studies. Routine antibody testing following vaccination is not recommended by the US Food and Drug Administration. Most commercial tests do not screen for neutralizing antibodies, the cut-offs for antibody detection are not necessarily the same as clinically relevant and there is no agreement on what antibody titre can be considered protective against SARS-CoV-2 infection. However, individual physicians and patients may decide that antibody testing is desirable following a discussion regarding the interpretation of the test results and the consequences/risks of acquiring COVID-19 infection.[14]

In summary, the immunological response to the vaccine is probably somewhat more complex than measuring antibody titre, as the T-cellular response and studies with long-term clinical follow-up are needed to assess efficacy in both preventing COVID-19 and severe disease, and safety. The issue of the third dose is a promising possibility and given the preliminary encouraging experience, deserves to be explored in future research. Also, the modification of immunosuppression, e.g. withdrawal of MMF in order to achieve a greater response, is a very controversial issue as the risk–benefit in relation to triggering rejection related to changes in immunosuppression is still unknown. Meanwhile, continued research, taking advantage of all available clinical data and evaluating immunogenicity, clinical efficacy and exploring strategies to improve vaccine response in vulnerable populations, such as HT patients, will help us to understand and control the COVID-19 pandemic.

Conflict of interest: none declared.

References

1. Latif F, Farr MA, Clerkin KJ, Habal MV, Takeda K, Naka Y, Restaino S, Sayer G, Uriel N. Characteristics and outcomes of recipients of heart transplant with coronavirus disease 2019. *JAMA Cardiol* 2020;**5**:1165–1169.
2. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;**383**:2603–2615.
3. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;**384**:403–416.
4. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, McCullough MP, Chappell JD, Denison MR, Stevens LJ, Pruijssers AJ, McDermott A, Flach B, Doria-Rose NA, Corbett KS, Morabito KM, O'Dell S, Schmidt SD, Swanson PA 2nd, Padilla M, Mascola JR, Neuzil KM, Bennett H, Sun W, Peters E, Makowski M, Albert J, Cross K, Buchanan W, Pikaart-Tautges R, Ledgerwood JE, Graham BS, Beigel JH; mRNA-1273 Study Group. An mRNA vaccine against SARS-CoV-2 – preliminary report. *N Engl J Med* 2020;**383**:1920–1931.
5. Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A, Lockhart S, Neuzil K, Mulligan MJ, Bailey R, Swanson KA, Li P, Koury K, Kalina W, Cooper D, Fontes-Garfias C, Shi PY, Türeci Ö, Tompkins KR, Lyke KE, Raabe V, Dormitzer PR, Jansen KU, Şahin U, Gruber WC. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med* 2020;**383**:2439–2450.
6. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, Garonzik-Wang JM. Immunogenicity of a single dose of SARS-CoV-2

messenger RNA vaccine in solid organ transplant recipients. *JAMA* 2021;**325**: 1784–1786.
7. Yi SG, Knight RJ, Graviss EA, Moore LW, Nguyen DT, Ghobrial RM, Gaber AO, Huang HJ. Kidney transplant recipients rarely show an early antibody response following the first COVID-19 vaccine administration. *Transplantation* 2021;**105**:e72–e73.
8. Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, Braun-Parvez L, Martzloff J, Perrin P, Moulin B, Fafi-Kremer S, Caillard S. Low immunization rates among kidney transplant recipients who received 2 doses of the mRNA-1273 SARS-CoV-2 vaccine. *Kidney Int* 2021;**99**:1498–1500.
9. Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D, Katchman E, Levi S, Houri I, Lubezky N, Shibolet O, Katchman H. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. *J Hepatol* 2021;**75**:435–438.
10. Itzhaki Ben Zadok O, Shaul AA, Ben-Avraham B, Yaari V, Ben Zvi H, Shostak Y, Pertzov B, Eliakim-Raz N, Abed G, Abuhazira M, Barac YD, Mats I, Kramer MR, Aravot D, Kornowski R, Ben-Gal T. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients – a prospective cohort study. *Eur J Heart Fail* 2021;**23**:1555–1559.
11. Eckerle I, Rosenberger KD, Zwahlen M, Junghanss T. Serologic vaccination response after solid organ transplantation: a systematic review. *PLoS One* 2013;**8**:e56974.
12. Peled Y, Ram E, Lavee J, Sternik L, Segev A, Wieder-Finesod A, Mandelboim M, Indenbaum V, Levy I, Raanani E, Lustig Y, Rahav G. BNT162b2 vaccination in heart transplant recipients: clinical experience and antibody response. *J Heart Lung Transplant* 2021;**40**:759–762.
13. 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**:661–662.
14. American Society of Transplantation, International Society for Heart and Lung Transplantation, American Society of Transplant Surgeons. Joint Statement about Vaccine Efficacy in Organ Transplant Recipients. 9 July 2021. https://ishlt.org/ishlt/media/documents/ISHLT-AST_SARS-CoV-2-Vaccination_7-10-21.pdf (19 July 2021).