Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Microbiology and Infection 27 (2021) 1070–1071

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Editorial

COVID-19 vaccination in solid-organ transplant recipients: generating new data as fast as possible, but taking clinical decisions as slow as necessary

Almost 18 months after the discovery of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the subsequent declaration by the WHO of the coronavirus disease 2019 (COVID-19) pandemic, the world continues to struggle with an unceasing number of infections and overloaded health systems. A reason for optimism is the advent of highly efficacious vaccines against SARS-CoV-2, developed within a record period using different technologies [1–3]. Among them, mRNA-based vaccines (BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna)) seem to be the most efficacious in preventing symptomatic infection, need for hospitalization and death [1,2]. mRNA-based vaccines have been initially used in patients at high-risk for COVID-19-associated complications, namely the elderly, patients with chronic conditions and immunocompromised patients. Solid-organ transplant (SOT) recipients seem to be associated with impaired outcomes of COVID-19, probably because of the disproportionate number of comorbidities present in these patients compared with the general population [4]. However, SOT recipients have not been included in phase II and III clinical trials evaluating the efficacy of SARS-CoV-2 vaccines, and they have been under-represented in studies assessing the effectiveness of these vaccines in real life [5].

Given the absence of data coming from randomized trials on the tolerability, immunogenicity and efficacy of SARS-CoV-2 vaccines in SOT recipients, data produced by observational cohorts are highly welcomed. In this issue of *Clinical Microbiology and Infection*, Rozen-Zvi et al. have evaluated the antibody responses to the BNT162b2 vaccine in a prospective cohort of 308 kidney transplant recipients [6]. After a median time of 28 days after receiving the second dose of the vaccine, only 112 (36.4%) patients had detectable antibody levels against the spike protein of SARS-CoV-2. Vaccine response was associated with the net state of immunosuppression: patients receiving lower doses of antimetabolites, no mechanistic target of rapamycin inhibitors and low calcineurin-inhibitor levels had higher chances of reaching a detectable antibody response. On the contrary, older age and impaired kidney function were, as expected, associated with a lower immune response. Four seronegative patients developed symptomatic SARS-CoV-2 infection, with three severe cases including one patient who died [6]. These results of impaired immunogenicity are similar to those seen in other recent cohorts of transplant recipients, including liver (47% seropositivity rate [7]), heart (49% [8]) and lung (18% [9]) transplant recipients. Patients receiving belatacept, a drug blocking the co-stimulation pathway and impairing B-cell and T-cell cross-talk, have shown the poorest responses with only 5.7% seropositivity rate in a cohort in France [10]. Overall, these results are in sharp contrast with the almost universal 100% response seen in phase I and II trials with mRNA-based vaccines in the general population.

What are the clinical implications that we can extract from these studies? The first message to convey is that these results are preliminary and that more research is needed to better establish the clinical relevance of this observation. Very few studies so far have evaluated cell-mediated responses in addition to humoral responses to the vaccine. Preliminary data suggest that patients who did not elicit antibodies against mRNA-based vaccines may develop some protection by cell-mediated immunity [11]. More importantly, data on the clinical efficacy of these vaccines in immunocompromised patients are still missing given the lack of data on the correlation between antibody levels and clinical protection. It is essential to know whether patients with undetectable responses may still be protected against severe manifestations of COVID-19, hospitalization and death. Previous studies suggest that despite lower antibody and cell-mediated immunity elicited in SOT recipients by influenza vaccine [12], vaccination has been robustly associated with lower rates of severe infection and influenza-associated complications [13]. Although some cases of severe breakthrough infections have already been reported in SOT recipients, including by Rozen-Zvi et al. [6,14,15], this can be expected even in immunocompetent individuals, as no vaccine is 100% efficacious against clinical disease [5]. In that regard, recent data in the general population suggest that individuals who develop SARS-CoV-2 infection after vaccination have lower viral loads and higher rates of asymptomatic infection than unvaccinated people who become infected [16]. All published studies so far have assessed the immunogenicity of mRNA-based vaccines, so that data are lacking on the immune responses using other vaccine platforms that are currently used in different parts of the world (such a viral vector-based, protein-based, and inactivated virus vaccines) specifically in the transplant population. Overall, large cohorts comparing the rate of infection in vaccinated and unvaccinated transplant recipients are still needed.

If this lower immunogenicity of the vaccine is confirmed, how can we improve the effectiveness of the vaccine in transplant recipients? Data from interventional research already performed in SOT recipients for influenza vaccine may help to delineate novel strategies for COVID-19 vaccination, namely the use of booster or higher

DOI of original article: https://doi.org/10.1016/j.cmi.2021.04.028.

https://doi.org/10.1016/j.cmi.2021.06.018

doses [17,18]. In one of the largest cohorts evaluating both BNT162b2 and mRNA-1273, a significant increase in antibody levels was observed after the second dose of the vaccine (from 18% to 56%) [19], so that the administration of a third dose of the vaccine seems to be the logical way of further boosting the immune response. Administration of a double dose (i.e. two simultaneous injections instead of one) may also potentially increase the immune response to the vaccine, although phase I and II trials with the mRNA-based SARS-CoV-2 vaccines did not show major differences in neutralization responses irrespective of the dose used [20]. Therefore, the safety and efficacy of these novel strategies should imperatively be tested in controlled trials. Another way of potentially reducing the negative effect of immunosuppression on vaccine response would be by modulating the levels of the immunosuppressive drugs, in particular by reducing the dose of mycophenolate immediately before and after vaccination. Again, given the potential risk for developing acute rejection with this strategy, this needs to be tested in the context of a clinical trial. The example of the research platform implemented by the Johns Hopkins University allowing the inclusion of patients all over the USA through a digital campaign [19], or the large number of published studies involving cohorts of vaccinated patients from Israel [6–9], shows that well-designed and adequately powered clinical trials can be rapidly implemented to answer these and other research questions.

While waiting for more data, what should we say to transplant physicians and patients? Given the potential lower efficacy of the vaccine, we should transmit a message of caution by continuing to follow the basic recommendations for protection, such as mask use, hand hygiene and social distancing. Routine use of serology for checking the response to the vaccine is not recommended at present, given the lack of approved cut-offs for protection and differences in the performance of the available serological assays. A negative result for serology can create undesirable anxiety to the patient; or in contrast, given the wide range of antibody titres observed in SOT recipients, a positive serology result may lead to a false sense of protection, in particular for these patients with low titres. Cocooning vaccination of household members should be strongly encouraged, as well as rapid testing in case of symptoms compatible with COVID-19, even in vaccinated individuals. But above all, we urgently need data from well-designed interventional research to fill the unknown gaps in order to apply evidence-based measures to better protect our transplant population [21].

Transparency declaration

OM have received grant support from Lophius Bioscience and Advisory Board fees from MSD and Gilead.

Funding

No external funding was received.

References

[1] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403–16.
[2] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020;383:2603–15.
[3] Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and efficacy of singledDose Ad26.COV2.S vaccine against COVID-19. N Engl J Med 2021. epub ahead of print.
[4] Danziger-Isakov L, Blumberg EA, Manuel O, Sester M. Impact of COVID-19 in solid organ transplant recipients. Am J Transplant 2021;21:925–37.
[5] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA COVID-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384:1412–23.
[6] Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atamna A, et al. Antibody response to mRNA SARS-CoV-2 vaccine among kidney transplant recipients – prospective cohort study. Clin Microbiol Infect 2021. https://doi.org/10.1016/j.cmi.2021.04.028. Online ahead of print.
[7] Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol 2021. epub ahead of print.
[8] Itzhaki Ben Zadok O, Shaul AA, Ben-Avraham B, Yaari V, Ben Zvi H, Shostak Y, et al. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplanted patients – a prospective cohort study. Eur J Heart Fail 2021. epub ahead of print.
[9] Shostak Y, Shafran N, Heching M, Rosengarten D, Shtraichman O, Shitenberg D, et al. Early humoral response among lung transplant recipients vaccinated with BNT162b2 vaccine. Lancet Respir Med 2021. epub ahead of print.
[10] Chavarot N, Ouedrani A, Marion O, Leruez-Ville M, Villain E, Baaziz M, et al. Poor anti-SARS-CoV-2 humoral and T-cell responses after 2 injections of mRNA vaccine in kidney transplant recipients treated with belatacept. Transplantation 2021. epub ahead of print.
[11] Cucchiari D, Egri N, Bodro M, Herrera S, Del Risco-Zevallos J, Casals-Urquiza J, et al. Cellular and humoral response after mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. Am J Transplant 2021. epub ahead of print.
[12] Hequet D, Pascual M, Lartey S, Pathirana RD, Bredholt G, Hoschler K, et al. Humoral, T-cell and B-cell immune responses to seasonal influenza vaccine in solid organ transplant recipients receiving anti-T cell therapies. Vaccine 2016;34:3576–83.
[13] Kumar D, Ferreira VH, Blumberg E, Silveira F, Cordero E, Perez-Romero P, et al. A 5-year prospective multicenter evaluation of influenza infection in transplant recipients. Clin Infect Dis 2018;67:1322–9.
[14] Wadei HM, Gonwa TA, Leoni JC, Shah SZ, Aslam N, Speicher LL. COVID-19 infection in solid organ transplant recipients after SARS-CoV-2 vaccination. Am J Transplant 2021. epub ahead of print.
[15] Caillard S, Chavarot N, Bertrand D, Kamar N, Thaunat O, Moal V, et al. Occurrence of severe COVID-19 in vaccinated transplant patients. Kidney Int 2021. epub ahead of print.
[16] Levine-Tiefenbrun M, Yelin I, Katz R, Herzel E, Golan Z, Schreiber L, et al. Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine. Nat Med 2021;27:790–2.
[17] Cordero E, Roca-Oporto C, Bulnes-Ramos A, Aydillo T, Gavalda J, Moreno A, et al. Two doses of inactivated influenza vaccine improve immune response in solid organ transplant recipients: results of TRANSGRIPE 1-2, a randomized controlled clinical trial. Clin Infect Dis 2017;64:829–38.
[18] Mombelli M, Rettby N, Perreau M, Pascual M, Pantaleo G, Manuel O. Immunogenicity and safety of double versus standard dose of the seasonal influenza vaccine in solid-organ transplant recipients: a randomized controlled trial. Vaccine 2018;36:6163–9.
[19] Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. JAMA 2021. epub ahead of print.
[20] Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 – preliminary report. N Engl J Med 2020;383:1920–31.
[21] CDC. Third dose of Moderna COVID-19 vaccine in transplant recipients. Available at: https://clinicaltrials.gov/ct2/show/NCT04885907?term=kumar&cond=covid+vaccine&draw=2&rank=1.

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19 May 2021
Available online 19 June 2021

Editor: L. Leibovici