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.

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Commentary

Precautions after vaccinating immunosuppressed patients with mRNA-based vaccines against SARS-CoV-2: does one size fit all?

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Phase III approval trials for the currently used vaccines for COVID-19 excluded immunocompromised patients. Therefore, vaccine efficacy data in this population are only available from real-life non-interventional studies, most assessing anti-SARS-CoV-2 antibodies after vaccination.

Studies of solid organ transplant (SOT) recipients show an overwhelming proportion of patients with inadequate antibody response, with most showing inverse correlation with the degree of immunosuppression. In a large US cohort including 658 SOT recipients, 46% of patients remained seronegative after two doses of mRNA-based vaccines, either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) [1]. In another study, among 308 kidney transplant recipients, 36% tested seropositive after the second dose of BNT162b2 vaccine [2]. Similarly, a 47% seropositivity rate was found among 80 liver transplant recipients fully vaccinated with BNT162b2 vaccine [3]: 49% among 37 heart transplant recipients [4], and only 18% among 168 lung transplant recipients [5]. Patients receiving specific immunosuppressive drugs such as belatacept seem to be at high risk of non-response [6]. Of note, very few data are available on the cell-mediated immune response to mRNA vaccines in SOT recipients, and as immunogenicity of the vaccines has not been fully assessed it may therefore be underestimated if only humoral immunity is evaluated.

Other immunocompromised patient groups were also assessed, with varying results. All 48 inflammatory bowel disease patients treated with biological therapy (mostly anti-tumour necrosis factor or anti-integrin) tested seropositive following one or two doses of either mRNA vaccine [7]. Fully vaccinated multiple sclerosis patients tested seropositive in 4% and 23% while treated with fingolimod or ocrelizumab, respectively. All patients receiving cladribine in this study had adequate antibody response [8]. Evaluation of 67 patients with haematological malignancies found that only 46% developed antibodies after vaccination, with the lowest proportion (26%) seen among patients with chronic lymphocytic leukaemia (CLL), most of them not on active treatment [9]. Among 167 CLL patients, 40% had adequate antibody response after full vaccination with BNT162b2, with only 16% response among patients under treatment at the time of vaccination. All patients treated with anti-CD20 drugs in the year prior to vaccination tested seronegative [10]. Data regarding antibody response after vaccination in patients with solid malignancies are lacking, but assessment of oncological patients who underwent positron emission tomography with computed tomography scan after vaccination demonstrated ipsilateral axillary lymph node uptake in only 45% of 377 patients, which was inversely associated with immunosuppressive treatments, perhaps suggesting a diminished immune response [11].

Although immunocompromised patients were excluded from all phase III vaccine approval trials and there is still lack of data as to the real-world clinical efficacy of the currently used vaccines, the data presented here are a source of concern. As countries are starting to ease social distancing restrictions, and as international travel is resuming, there is an urgent need to identify the specific

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populations at risk of being under-protected after receiving SARS-CoV-2 vaccines. Although antibody response may not fully represent the actual disease-preventing mechanism of mRNA-based vaccines, we suggest that patient populations shown to mount diminished post-vaccination humoral responses (including SOT recipients, CLL patients and those receiving anti-CD20 therapy) should continue practising social distancing and use personal protective equipment during close encounters. Additional studies should further characterize patient groups with diminished immunogenicity. Furthermore, we should try applying strategies that may improve vaccine immunogenicity in those populations. Use of vaccines other than those based on mRNA technology, additional vaccine booster dosage or increasing the vaccine dose and temporary immunosuppression reduction prior to vaccination may be such strategies that should be carefully evaluated in the context of clinical trials. Prioritizing patients for vaccination before starting immunosuppression should be considered, if possible; and vaccination of household members and close contacts of immunosuppressed people should be strongly perused. First attempts in applying new strategies in immunosuppressed people have been recently published in two papers, in which organ transplant recipients received a third dose of the BNT162b2 vaccine. In a study by Massa et al. [12], 61 kidney transplant recipients have only had mild reactions to the third vaccine dose, while showing an increase in both humoral and cellular responses, with an increase in seroconversion from 44.3% after the second dose to 62.3% after the third dose. A study by Kamar et al. [13] assessed the humoral response of 101 SOTs, with 40% of SOT recipients having anti-SARS-CoV-2 antibodies after the second BNT162b2 vaccine dose compared with 68% 4 weeks after the third dose, with no serious adverse events reported in any of the SOT recipients.

In conclusion, emerging data from the global vaccine effort have shown diminished antibody response in certain immunosuppressed populations, depending on underlying disease and type of immunosuppression. We suggest that the most vulnerable populations would be identified in ongoing, large-scale vaccine follow-up programmes, and that people who belong to those populations continue to practice special precautions as long as the COVID-19 pandemic is ongoing. Further research is needed to assess the immunogenicity of other non-mRNA-based vaccines among immunocompromised patients, characterize cellular immune response to vaccination and define the correlation between immune response and actual risk of infection, including severe outcomes. We also suggest continuing research already being conducted using alternative vaccine regimens in a controlled manner in those populations, in order to improve protection against SARS-CoV-2.

Transparency declaration

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Author contributions

N.T. and D.Y. drafted the manuscript. All authors edited the final manuscript and approve its contents.

References

[1] 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;325:2204–6.
[2] 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;27:1173.e1–e4.
[3] 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;75:435–8.
[4] 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. https://doi.org/10.1002/ejhf.2199. PMID: 33963635. In press.
[5] 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;9. e52–3.
[6] 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;105:e94–5. https://doi.org/10.1097/TP.0000000000003784.
[7] Wong S-Y, Dixon R, Pazos VM, Gnjatic S, Colombel J-F, Cadwell K. Serological response to mRNA COVID-19 vaccines in IBD patients receiving biological therapies. Gastroenterology 2021;161:715–8. e4.
[8] Achiron A, Mandel M, Dreyer-Alster S, Harari G, Magalashvili D, Sonis P, et al. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. Ther Adv Neurol Disord 2021;14. 17562864211012836.
[9] Agha M, Blake M, Chilleo C, Wells A, Haidar G. Suboptimal response to COVID-19 mRNA vaccines in hematologic malignancies patients. MedRxiv 2021. PMC8043479.
[10] Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood 2021;137:3165–73.
[11] Eifer M, Tau N, Alhoubani Y, Kanana N, Domachevsky L, Shams J, et al. Covid-19 mRNA vaccination: age and immune status and its association with axillary lymph node PET/CT uptake. J Nucl Med 2021. https://doi.org/10.2967/jnumed.121.262194. PMID: 33893188. In press.
[12] Massa F, Cremoni M, Gerard A, Grabsi H, Rogier L, Blois M, et al. Safety and cross-variant immunogenicity of a three-dose COVID-19 mRNA vaccine regimen in kidney transplant recipients. Rochester, NY: Social Science Research Network; 2021.
[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;385:661–2.