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COMMENTARY

Is a third SARS-CoV-2 vaccine dose efficient in allogeneic haematopoietic cell transplant recipients?

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When and how often should allogeneic haematopoietic cell transplantation recipients be vaccinated against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is unclear. The report by Bankova et al. suggests that a third SARS-CoV-2 vaccine dose is important but still insufficient in some patients to establish an adequate humoral response.
Commentary on: Bankova et al. Antibody response to a third SARS-CoV-2 vaccine dose in recipients of an allogeneic hematopoietic cell transplantation. Br J Haematol. 2022 (Online ahead of print). doi: 10.1111/bjh.18562. xxx

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In their paper the authors report on the humoral response to a third dose of messenger RNA (mRNA) severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine in recipients of an allogeneic haematopoietic cell transplantation (allo-HCT). Allo-HCT recipients are severely immunocompromised and due to a waning of pathogen-specific immunity after HCT need to be re-immunised for vaccine-preventable diseases. SARS-CoV-2 vaccinations became an important part of the post-HCT vaccination programme, and their safety and immunogenicity in this special patient population has been assessed in several prospective clinical trials.[1–3] When and how often should allo-HCT recipients be vaccinated against SARS-CoV-2 remains an open issue.

In their initial report, the authors analysed humoral responses after two vaccine doses in a relatively large cohort of 110 allo-HCT recipients.[3] Only 62% of transplant patients had detectable neutralising antibody (Ab) titres at 1 month after the second mRNA vaccine, as compared to the 100% response found in 86 healthy controls. As expected, there was a rapid decline of Ab titres both in patients and healthy controls. Factors associated with impaired Ab responses in the allo-HCT recipients were older age >65 years, ongoing immunosuppression (IST) and disease relapse. On the other hand, priming vaccination in patients at later time-points after allo-HCT (>12 months) led to better humoral responses, as compared to those who were vaccinated earlier (3–12 months) after HCT, indicating the role of immune regeneration for efficient vaccine response.[2,4] Still, due to the concern of breakthrough infections in this very fragile patient population, current guidelines favour the start of vaccination as early as 3 months after HCT.

It is now commonly accepted that a third vaccination is required to fully vaccinate. The study by Bankova et al. builds on their previous work and presents follow-up evaluation of the same cohort of patients and healthy controls after they received the third vaccination dose against SARS-CoV-2. Ab titres were assessed in 74 allo-HCT recipients and 62 healthy controls at 1 month after a third mRNA vaccine. There was a significant increase in Ab levels in both groups, with 77% of transplant patients and 100% of healthy controls achieving sufficient neutralisation activity. To elucidate the improving effect of the third vaccination in the transplant patients, the authors focused on 22 patients who had low Ab titres after two vaccinations. From these, 50% (11 patients) responded adequately

to the third vaccine and the other half remained low responders. Patients who were no longer on IST had the better chance to seroconvert after the third vaccine dose. This finding is not unexpected and has been already reported by others[5] but may serve to guide timing for the next vaccine dose if the patient condition and epidemiological situation allow delaying the vaccine. Other factors that have been reported to negatively influence vaccine responses after a third dose in allo-HCT recipients are low B-cell counts and use of haploidentical donors.[6,7]

What can the data of Bankova et al. tell us? Although a third vaccine dose in allo-HCT patients led to a significant improvement of the humoral immune response, some (>20%) of them still do not seroconvert. The results of Bankova et al. help us to better identify such patients at risk of failing to respond and who are in need of other preventive measures. Using longitudinal Ab measurements and distinguishing different patterns of immune reconstitution might provide an elegant way to efficiently guide timing of vaccinations. As of now, such strategies are still not standardised and remain somewhat impractical due to their costs and complexity. An important question that remains unexplored by the authors is the SARS-CoV-2-specific T-cell response after serial vaccination. In particular, it will be of a great interest to assess if transplant recipients who lack humoral response still develop vaccine protection through cellular immunity, and most importantly how both humoral and cellular responses might be affected by different IST regimens.

Lastly, the authors report, that 15 of 52 (28.8%) transplant recipients had a SARS-CoV-2 infection, but none required hospitalisation or died due to the infection. It is comforting, that in the era of predominating Omicron variants, vaccinations, efficient treatments with antibodies and antiviral drugs, and pre-exposure prophylaxis, severe disease courses of coronavirus disease 2019 (COVID-19) have become rare and most patients, even the immunocompromised transplant recipients, can be managed without major complications and with low mortality rates.

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