Serological response following anti-SARS-CoV-2 vaccination in hematopoietic stem cell transplantation patients depends upon time from transplant, type of transplant and "booster"dose

We read with great interest the systematic review and meta-analysis by Gagelmann *et al.* on antibody response after vaccination against SARS-CoV-2 in adults with hematological malignancies recently published in Haematologica.[1] Among others, the authors analyzed thirteen studies evaluating 1,324 patients who had undergone hematopoietic cell transplantation (HSCT). The pooled response was 83% for autologous and 82% for allogeneic HSCT recipients, respectively. Though limited evidence showed higher responses for patients receiving vaccination at least 6-12 months after HSCT, the analysis was not able to differentiate the results according to specific timing and type of transplantation, an aspect that was not systematically assessable, due to the low number and heterogeneity of studies.

We recently published a prospective, cohort study,[2] not included in the meta-analysis, of 114 fully vaccinated patients who had received an autologous (52 patients) or allogeneic (62 patients) HSCT at least 3 months before the first dose of vaccination. Overall, serological response rate (>50 AU/mL of anti-spike protein immunoglobulin G [IgG] antibodies detected 4 weeks after the second dose of BNT162b2 mRNA COVID-19 vaccine) was 84%, thus perfectly in line with the results of the meta-analysis. Interestingly, responders after an allogeneic HSCT performed better, in terms of magnitude of serological response, than those treated with an autologous HSCT. However, 6% of autologous and 24% of allogeneic HSCT recipients did not respond at all. In that study, aiming to explore in depth the response according to the time elapsed from transplant, we stratified the patients into three groups: G1=<1 year; G2=1-5 years; G3=>5 years. Among 16% of patients who failed to respond, the large majority was constituted of individuals transplanted within 1 year before vaccination and who had received an allogeneic HSCT. When compared to 107 healthy controls (HC) matched for age and sex, lower antibody titers were observed in both allogeneic and autologous HSCT recipients in G1, while no differences emerged in G2. Interestingly, results in G3 between HC and allogeneic recipients were comparable, whereas patients in the autologous subgroup showed significantly lower titers than HC.[2]

Thus, we confirmed that most of transplanted patients respond to a complete vaccination cycle and we also observed that failures generally occur within the first year from transplant, mainly in allogeneic HSCT recipients. Furthermore, our analysis revealed that patients who had received an allogeneic transplantation develop higher antibody production than those who had received an autologous transplantation, particularly if vaccinated more than 5 years after HSCT.

Time requested for a quantitative and functional recovery of B and T cells after HSCT (up to 1 year or even more), as well as the use of graft-*versus*-host disease prophylaxis with immunosuppressive agents in the allogeneic setting, might explain the lower antibody titers and the larger number of non-responders in G1. Differences between autologous and allogeneic groups in patients transplanted more than 5 years before vaccination might be instead related to a more frequent persistence of a still active disease and to ongoing salvage treatments in autologous HSCT recipients, which are well known risk factors for a poor response to vaccination.[1] For example, our experience confirmed that patients with myeloma in remission phase after autologous HSCT show significantly higher antibody titers than patients with active disease.[2] On the other hand, we hypothesize that the presence of a "healthy" and consolidated immune system provided by the donors in the allogeneic setting, could play a role in producing a more robust response after a longer time period, like that in normal individuals, as we observed in our patients.

Administration of a "booster" dose could change such a scenario. Recent data suggest that a third dose of BNT162b2 anti-SARS-CoV-2 mRNA vaccine may improve the humoral response in allogeneic HSCT recipients.[3,4] Some preliminary data from our Institution also indicate a significant increase of serological response after a third dose of BNT162b2 anti-SARS-CoV-2 mRNA vaccine in transplanted patients, particularly, but not only, in the allogeneic group. Of note, a not negligible proportion of non-responders after the first two doses (mainly patients belonging to the allogeneic HSCT group in G1, more rarely in the autologous setting) was able to mount a serological response 1 month after the third dose (Attolico *et al.*, manuscript in preparation).

Most of the available studies have only evaluated the serological response in terms of anti-spike IgG antibodies. Clear-cut relationships between these antibodies and protection against the virus has not been unequivocally established. As observed in other contexts, neutralizing antibodies, development of memory B cells and T-cell immune response after vaccination could play an even more important role in protecting against SARS-CoV-2 infection. Notwithstanding, we underline that time from transplant, type of transplant (allogeneic *vs.* autologous) and a third dose of vaccine significantly affect the serological response in HSCT patients. If further confirmed in larger studies, we think these aspects should be considered in planning anti-SARS-CoV-2 vaccine strategies for these patients.

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