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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The Bottom Line

Beginning to understand clinical events and immune responses of hematopoietic cell transplant recipients receiving SARS-CoV-2 vaccination

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The clinical strategy of vaccination for severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is a preventative therapy authorized by the Food and Drug Administration (FDA) under Emergency Use Authorization (EUA), and is the most important development in the fight against the SARS-CoV-2 pandemic. Patients with hematological cancers are at increased risk of severe coronavirus disease and death [1]. The development of two mRNA vaccines [2] and an adenovirus vaccine [3] represents SARS-CoV-2 technology that has been studied in healthy adults. There is not a specific vaccine for immune compromised transplant recipients. EUA authorized therapies can only be used as authorized. By studying hematopoietic cell transplant (HCT) recipients who are using the vaccines now, as authorized, we can learn information to contribute to the next wave of the pandemic or the next respiratory virus season.

In a recent issue of Transplantation and Cellular Therapy, Ali and colleagues reported on the "Safety and Tolerability of SARS-CoV-2 Emergency-Use Authorized Vaccines Allogeneic Hematopoietic Stem Cell Transplant Recipients" [4]. This study reviewed adverse effects following vaccination among 113 HCT patients, as well the incidence of new onset chronic graft versus host disease (GVHD) (9.7%) or worsening of existing GVHD (3.5%). Vaccines were well-tolerated regarding short term issues.

The FDA has specifically issued guidance not to test patients with serology to determine whether there is protection. Not all tests have the same performance, the protective threshold is yet to be determined, and targets of assays are different and may not correlate with neutralization. If patients are aware of a positive serology response, would they assume they have protection and reduce their precautionary stance? However, in a research setting, this information contributes to our understanding of SARS-CoV-2 vaccination.

In a recent issue of Transplantation and Cellular Therapy, Easdale and colleagues reported on "Serologic Responses following a Single Dose of SARS-Cov-2 Vaccination in Allogeneic Stem Cell Transplantation Recipients" [5]. Fifty-five allogeneic HCT recipients had reached the 3 month mark following transplantation. Serologic response was 58% for patients no longer receiving immunosuppression, versus 21% for those on systemic immunosuppression.

In this issue of Transplantation and Cellular Therapy, Ram and colleagues report on the "Safety and Immunogenicity of the BNT162b2 mRNA Covid-19 Vaccine in Patients after Allogeneic HCT or CD19-based CART therapy – a Single Center Prospective Cohort Study" [6]. The number of patients evaluated in this single center study from Israel, 66 allogeneic HCT recipients and 14 chimeric antigen receptor T cells (CAR-T) patients, is relatively small. Vaccination could commence as early as 3 months after cell infusion, although vaccination was deferred to 6 months for low numbers of CD19+ cells or until stabilization of GVHD. The immunity follow-up was assessed 1-2 weeks after the second vaccine dose. In the Ram study, positive serology was documented in 75% (47 of 57 tested) of patients following allogeneic HCT and 36% (5 of 14 tested) of patients after CAR-T infusion.

On multivariate analysis, a positive humoral response to the vaccine was associated with increased time from infusion of cells (p=.032), female sex (p=.028), and higher number of CD19+ cells (p=.047) [6]. The gender finding is different from the Sharma report, a cohort of 184 allogeneic and 134 autologous HCT recipients [7]. In this study, risk factors for increased mortality following COVID-19 among allogeneic HCT recipients included age $\geq$ 50 years (p=0.020), male sex (p=0.006), and $\leq$ 12 months from allogeneic HCT (p=0.005). Gender was not an association with Covid-19 severity or mortality for 58 patients in the Mushtaq cohort [8].

There is more to protection by vaccination than measurement of antibodies. In the Ram study, an ELISpot assay looked at the detection of peptide-induced interferon-gamma and interleukin-2 secretion. CAR-T patients with B cell reconstitution had a higher incidence of positive serology when compared to those with B cell aplasia. However, three CAR-T patients with negative serology showed cellular response with positive ELISpot results, yet all three patients had complete B cell aplasia. In summary, 57% (8 of 14 tested) patients after CAR-T infusion had either humoral or cellular response to the vaccine. I would agree with the authors' conclusions that B cell

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aplasia by itself should not preclude patients from starting a vaccine series.

In the Ram study, antigen presenting cells, macrophages and monocytes, looked at the ability of convalescent donor T cells to process and present, or recognize, viral peptides. Positive and negative controls were good. Stimulation of membrane glycoprotein had the strongest response when compared to viral spike glycoprotein and nucleocapsid protein, those targets usually evaluated in serology assays. No vaccine is perfect, but this testing indicates that SARS-CoV-2 vaccination of HCT recipients and CAR-T infusions provides otherwise unmeasured and under recognized benefit to some patients.

The authors' choice of study design excluded patients with relapse of malignancy, those taking high-dose steroids for uncontrolled GVHD, a lack of remission following CAR-T therapy, or the development of SARS-CoV-2 infection following the first dose of vaccine. Cellular response was tested for only half of the enrolled patients. What clinicians should take away from this study is that there is no clear definition of what level of humoral response correlates with clinical protection. Different laboratory tests do not necessarily correlate well. Predictors of cellular response should be interpreted with caution. In addition, there is a need to study those participants enrolled in immunity studies who do and do not develop infection.

We will benefit from research extending the length of time after completion of the vaccine series for which vaccine responses are tested. The question of persistence of immunogenicity is not addressed within the Ram study. Prospective longitudinal monitoring of immunity studies can take place using established research repositories, such as the Covid-19 vaccine immunity study ongoing as part of the Center for International Blood and Marrow Transplant Research protocol under ClinicalTrials.gov identifier NCT01166009. One goal of this in-process study is to see if immunogenicity and the durability of immunogenicity is higher among patients receiving vaccination 6-12 months after HCT or CAR-T, when compared to those vaccinated earlier. As in the Ram study, the study plans to describe vaccine-related adverse events and GVHD.

In conclusion, vaccines reduce morbidity and mortality from infection, in addition to reducing the incidence of disease associated with infection. Vaccinating large portions of the population is the best medicine for our patients, and we will benefit from research into the protective effect of vaccine responses. Published measures to prevent infections primarily transmitted through respiratory exposures remain relevant to our patients [9]. Prospective studies of immune responses to vaccines for SARS-CoV-2 infection will provide clinicians with valuable data to counsel patients regarding immunity to infection, address questions regarding timing of vaccines, and in general allow for less uncertainty for patients, their caregivers, and their HCT and CAR-T providers.

POTENTIAL CONFLICTS OF INTEREST

J.H.Y. is a co-investigator for the Center for International Blood and Marrow Transplant Research study under ClinicalTrials.gov identifier NCT01166009.

J.H.Y. reports that The University of Minnesota is paid on a per-subject basis to cover the costs of enrolling subjects on clinical trials unrelated to coronavirus infections, for AlloVir, Astellas, Ansun, Cidara, Janssen, Merck, NobelPharma, ReViral, Scynexis, and Shire/Takeda, outside the submitted work.

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