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CLINICAL TRIALS AND OBSERVATIONS

Comment on Ghione et al, page 811

The next wave: immunizing the immunosuppressed

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In this issue of *Blood*, Ghione et al report important early results on the differential development of antibodies to SARS-CoV-2 after vaccination in patients with lymphoma who were receiving B-cell–directed therapies.[1] These data add to information recently reported by Terpos et al[2] on antibody response to vaccination in older patients with multiple myeloma (MM).

Unfortunately, the results confirm what we feared—that many of our patients will not achieve immunoglobulin G (IgG) antibody responses from the coronavirus vaccination.[3] The letters both emphasize that we still have much to learn about the complex interactions between preventative inoculation strategies in patients with disease or treatment-related immunosuppression.

Clinical researchers have been highly motivated to quickly determine the efficacy of current vaccination efforts in patients with diseases such as MM and in patients who are immunocompromised. The clinical question posed by Terpos et al[2] was: how much response one can expect from a single dose of the BNT162b2 messenger RNA (mRNA) vaccine? With the supply of vaccines in question and international pressure to defer second doses for people who were not in priority groups until members of priority groups had received at least one dose,[4,5] researchers wondered whether just 1 dose would generate an adequate response in patients with MM. By using the 50% neutralizing antibody titer as a threshold for clinically relevant viral inhibition, these investigators demonstrated that only about 10% of patients with MM reach an adequate level of protection after the first vaccination. Their data suggest that immunoparesis of at least 1 uninvolved immunoglobulin may be the reason for failure to respond to the initial vaccination. Indeed, as the authors pointed out, hypogammaglobulinemia has been associated with inferior antibody response to coronavirus among patients with chronic lymphocytic lymphoma (CLL). Notably, the older individuals who served as controls in their study were also poorly protected after a single vaccination; only 20.2% achieved clinically relevant viral inhibition before they received the second dose. A

The article by Ghione et al focuses on patients with lymphomas and assessed antibody levels after full vaccination. The patients were divided into 4 cohorts based on time since treatment with B-cell–directed therapy, with health care workers and nursing home residents serving as controls. The researchers found that IgG responses were significantly different, depending on the length of time since treatment. Of the 52 patients with B-cell lymphoma who were vaccinated within 9 months of B-cell–directed treatment, only 6 (11%) developed a humoral response, whereas 22 of 25 patients who had a treatment-free interval of 9 months or more before they were vaccinated were able to develop IgG antibodies. The takeaway here is that there may well be a minimum interval for immune reconstitution after B-cell–directed therapy, an interval that could be used in an effective revaccination protocol.

Immunosuppressed individuals have faced special peril with this pandemic all along. The severe infection rates and morbidity for patients with hematologic malignancies are higher than those with other forms of malignancy.[6] Whether this vulnerability is a result of higher rates of infectivity, disproportionately poor response to therapy, comorbidities, or provider nihilism remains an open question. With the excellent efficacy rates of most of the approved vaccines, no one is advocating against vaccination, even in those who may not adequately respond.[7] Rather, these data emphasize the importance of maintaining infection control practices even after our patients have been vaccinated.

For years, there have been reports of inadequate immune response to vaccination in patients with CLL, MM, and other conditions associated with immune deficiency.[8] After autologous allogeneic transplantation, patients have severely reduced antibody titers, and they subsequently undergo broad spectrum vaccinations after transplantation. Consensus guidelines have regularly been published to help manage this population, but even those guidelines point out the significant holes in the data.[9]

What we don't know is evident in the letter from Terpos et al[2] and the article by Ghione et al. What are the best predictors of response in patients? How much antibody is enough to prevent severe infection? In the absence of humoral response, can cellular response provide protection? In regions where herd immunity has not yet been achieved, which treatments should be deferred? Should titers be measured in everyone? Will revaccination or booster shot strategies work?

Large-scale studies designed to provide answers to some of these questions are underway, although it is anticipated that the lessons from Ghione et al and Terpos et al[2] will prove true even in much broader populations. Meanwhile,

clinicians are responsible for informing their patients that they may well remain at risk and that their best options include making sure that their families and contacts have been vaccinated and otherwise continuing to adhere to social distancing and mitigation strategies. The data provided by Terpos et al and Ghione et al reveal important unknowns, questions we need to address for this pandemic and for the next one.

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