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EDITORIAL

Diversity of antibody responses after influenza infection or vaccination—Needed or nice to have?

Influenza is a major threat in solid organ transplant recipients with significant morbidity and mortality.[1] Yearly vaccination is therefore key to convey protection toward the circulating strains, and to prevent severe disease. In addition, natural exposure and regular vaccination may contribute to an increasing diversity of the immune response by accumulation of cross-protective immunological memory toward different strains. Unfortunately, vaccination in transplant recipients is challenging due to suboptimal vaccine efficacy which is significantly lower than in the general population.[1] Thus, efforts toward improving vaccine responses will benefit from a detailed knowledge on the diversity of the immune response conveyed by vaccines or natural infection.

In this issue of the journal, a microarray assay including a panel of 86 selected antigens was used to compare boosting of humoral IgA and IgG immune responses in 40 transplant recipients after vaccination with a trivalent standard-dose split vaccine with two groups of 40 patients after H1 N1 and H3 N2 infection, respectively.[2] For each antigen, the change of antibodies was quantified 4 weeks after vaccination or disease onset as fold change from baseline levels. Of note, the number of antigens that elicited an antibody response was higher after wild-type infection than after vaccination. Among infected patients, antibodies were mainly directed against proteins of the infecting subtype. Interestingly, heterosubtypic responses toward antigens from other strains were also found, which may have been favored by sequence similarity among antigens from related strains. Comparative clustering analysis further revealed that antigens with highest antibody increase clustered among infected patients. Thus, the markedly different antigen response patterns between infected and vaccinated patients led the authors to conclude that the limited breadth of antigen specificities in vaccinated patients may be a cause for the suboptimal vaccine efficacy in transplant recipients. However, as similar data have been observed for immunocompetent individuals,[3] immunodeficiency is unlikely the primary cause.

The differences in breadth may result from differences between wild-type virus and vaccine as well as from the study design and selection of patient groups. Reference strains for vaccine production are reassortant viruses where only hemagglutinin and neuraminidase correspond to the yearly recommended wild-type strains. All other components originate from a laboratory-adapted A/PR/8/34 strain with the ability to grow to high titers in embryonated eggs. Thus, although all major antigens are included in split vaccines, their diversity is limited toward hemagglutinin and neuraminidase. Another factor contributing to differences in antigen diversity may result from the fact that patients with infection were recruited between 2010 and 2015, whereas vaccinated patients were included in a single season after vaccination with the trivalent 2016/2017 split vaccine. Thus, unlike vaccine responses limited to three strains in one season, the higher diversity of antigen specificities in infected individuals may be a reflection of a higher diversity of viral or vaccine strains encountered over a period of five seasons.

Reasons for the marked differences in the fold increase in antibody levels in patients after infection and vaccination may result from lower immunogenicity of split vaccines, which decreases during the inactivation process. In contrast, wild-type viruses are naturally adjuvanted and trigger toll-like receptors by various means, as exemplified by double-stranded RNA occurring during infection only. Moreover, induction of antibodies may be stronger in patients after infection, who by definition had inappropriate protective immunity at baseline. It is well known that the induction is more pronounced in individuals with poor or without preexisting immunity, whereas a booster effect is weak in individuals with preexisting immunity.[4] Thus, two possibilities may explain the low increase among vaccinated patients. Apart from vaccine failure, this may indicate sufficient preexisting immunity where further boosting upon encounter with the vaccine strains was dispensable. Thus, the limited breadth and strength in specific immunity should only cautiously be interpreted as a correlate of poor vaccine efficacy.

What can we learn from this study for development of vaccines toward influenza and other viruses including SARS-CoV-2? Several more efficient influenza vaccines are available which are recommended for transplant recipients. Those include high-dose or more strongly adjuvanted vaccines, which are hypothesized to elicit a broader and stronger immune response. Interestingly, the vaccinated patients analyzed in this study originated from a randomized controlled trial comparing standard-dose versus high-dose vaccines.[5] As high-dose vaccination was shown to be an independent factor associated with seroconversion,[5] we encourage the authors to extend the microassay analysis to the high-dose group to evaluate their ability toward inducing a more diverse vaccine response. Likewise, microassays could be employed to comparatively study immunity after vaccination with recombinant or adjuvanted vaccines with natural immunity. Concerning SARS-CoV-2, immunity after natural

infection is directed against a variety of viral antigens. Despite this breadth in immunity after infection, the first licensed COVID-19 vaccines with remarkably high immunogenicity and efficacy are directed against the spike protein only. Since SARS-CoV-2 is newly introduced into the human population, the strain diversity is by far not as pronounced as for influenza, but is rapidly increasing. Thus, similar to influenza, this may result in immune escape variants, that will continue to challenge vaccine development toward this newly emerging virus.

KEYWORDS

editorial / personal viewpoint, infection and infectious agents - viral, infection and infectious agents - viral: influenza, infectious disease, monitoring: immune, vaccine

DISCLOSURE

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