ANTI-PD-1 THERAPY ALTERS THE GENERATION AND DURABILITY OF DE NOVO RESPONSES TO VACCINATION IN HUMANS

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Background Although anti-PD-1 expands pre-existing tumor-specific T cell responses, preclinical models of infection and vaccination suggest that early PD-1 pathway blockade may preferentially expand effector cells at the expense of memory cell or immunoglobulin generation. This has important ramifications for cancer immunotherapy combinations, as the timing of anti-PD-1 administration, may impact the generation and durability of de novo immune responses—a question that has not been tested in humans. Here, we tested the impact of anti-PD-1 on immune responses following SARS-CoV-2 vaccination.

Methods We collected PBMC and serum from healthy controls (n=30) and patients on anti-PD-1/L1 monotherapy (n=18) or anti-PD-1/combo combination therapy (n=14) every 1–2 months over a 6+ month period following Pfizer/BioNTech or Moderna SARS-CoV-2 mRNA vaccine without prior SARS-CoV-2 infection. Using a high-throughput, multiplexed Luminex array, we measured binding of antibody subtypes (IgG, IgG1, IgG2, IgG3, IgA1, IgA2, IgM) to bead-antigen conjugates encoding total spike, S1 subunits, (RBD, NTD) and S2 from the vaccine, variants of concern (alpha, beta, delta, omicron), and previously encountered antigens (CMV, tetanus, influenza). We also tested the antibodies’ capacity to engage Fc receptors or to initiate Fc function (phagocytosis).

Results Subjects treated with anti-PD-1 monotherapy had lower peak levels of vaccine sequence spike-specific IgG1 Ab compared to controls (Wilcoxon, p=0.0042). A similar effect was seen for the S1 and S2 subunits and variants of concern against IgG1. There were no differences in peak antibody responses against the other antibody subtypes (e.g IgG2, IgG3, IgM). Longitudinal analysis of IgG1 antibodies recognizing vaccine-derived spike declined over time for the control group whereas the antibody levels for the anti-PD-1 group showed no decline (ANOVA, F = 9.53, p = 0.00382). Binding of SARS-CoV-2 antibodies to Fc gamma receptors and phagocytosis by monocytes mirrored the trends seen for direct antigen binding. No difference was seen in immunoglobulin levels at peak or over time for CMV, tetanus, or influenza between treatment groups.

Conclusions Anti-PD-1 modulates de novo production of spike-specific IgG1 following SARS-CoV-2 vaccination but has no effect on pre-existing humoral immunity. Similar trends seen with variants of concern, Fc receptor binding and phagocytosis, suggest that anti-PD-1 may modulate antibody levels but preserves overall cross-reactivity and non-neutralizing antibody function. The longitudinal differences in IgG1 levels may suggest that anti-PD-1 treatment modulates formation of short-lived or long-lived antibody producing cells. Our work demonstrates that administration of anti-PD-1 alters the peak levels and kinetics of de novo humoral responses.

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