Immune Checkpoint Inhibitors (ICIs) on Patients With Hepatitis B Virus Infection: A Promising Approach for Achieving HBsAg Loss

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In Asia, since hepatitis B occurs at an early age, Chronic Hepatitis B (CHB) and viral persistence seem more frequent.[1] Many important factors, such as the genotype, the age of the infected individual, as well as the stage of the disease, could affect the immune response to therapy. There is evidence that activation of immunity can clear the virus. A high frequency of activated, intrahepatic HBV-spesific CD8+ T cells, combined with peripheral cytotoxic T cells that produce cytokines and expand, correlates with HBV control. Patients who controlled HBV after long-term Nucleoside/nucleotide analogue (NUC) therapy had T-cell frequencies similar to those of patients who resolved acute infections.[2] Higher frequencies of HBV-specific T cells in the blood might also correlate with controlled HBV rebound in patients who stopped taking NUCs.[3] T-cell Programmed Cell Death 1 (PD-1) expression correlated with a limited increase in alanine aminotransferase in patients who stopped taking NUCs,[4] suggesting that the activity of hepatic T cells is regulated to preserve liver function.[5]

In patients with chronic HBV infection, exhausted virus-specific CD8+ T cells, resulting from the activation of the PD-1 and programmed death ligand 1(PD-L1) axis, play a key role in the chronicity of infection. Functional cure for HBV, defined as the seroclearance of hepatitis B surface anti gen (HBsAg), is viewed as the optimal goal of chronic HBV infection treatment because HBsAg loss is associated with a low risk of hepatocellular carcinoma and a relatively favorable prognosis.[6]

T CELL EXHAUSTION IN CHRONIC VIRAL INFECTION

T cell exhaustion is a term that describes the hyporesponsive state of effector T cells during chronic antigen stimulation in the setting of chronic viral infections or cancer and appears to result from the accumulation of multiple signals or pathways that negatively regulates T cell responses. Viruses employ different strategies to establish chronic infections, namely continuous replication and latency.

Exhausted T cells (Tex) are by now referred to as a unique immune cell type. Tex are defined by loss or partial loss of effector functions and proliferative potential, expression of multiple inhibitory receptors, skewed metabolism, and an altered epigenetic and transcriptional program. More severely exhausted T cells further lose their ability to produce TNF and IFNy and to degranulate and the final state of T cell exhaustion is their physical deletion.[7] While inhibitory receptors are transiently upregulated during CD8+ T cell responses in acute, self-limiting viral infections, prolonged high-level expression of inhibitory receptors is a hallmark of exhausted T cells.[8] One important and the most prominent inhibitory receptor is PD1. Blocking PD1 signaling during chronic Lymphocytic choriomeningitis virus (LCMV) infection and HBV reinvigorated exhausted CD8+ T cells and resulted in a lower viral load.[9,10,11.]

IMMUNE CHECKPOINT INHIBITORS (ICIS)

PD1 is a check point on T cells. ICIs represent a key component in the treatment of cancer because they are associated with substantial improvements in the outcomes and long-term survival of patients with cancer. Various ICIs have been developed—for example, antibodies targeting PD-1 (eg, nivolumab), PD-L1 (eg, atezolizumab and durvalumab), and cytotoxic T-lymphocyte-associated protein 4 (eg, tremelimumab).[12] ICIs are now used in numerous cancer treatments, including unresectable Hepatocellular Carcinoma (HCC).

IMMUNE CHECKPOINTS WITH CHRONIC HBV INFECTION

PD-1/PD-L1 blockade can restore the function of liver-infiltrating HBV-specific T cells.[13] HBV peptide stimulation enables intrahepatic and peripheral T cells to produce both IFN-γ and interleukin-2. Anti-PD-1 treatment can restore the function of T cells to secrete IFN-γ and control HBV infection.[14,15]

ICIs AND HBSAG LOSS

Various anti-HBV drugs, such as ICIs, have been developed to eliminate HBsAg.[16] In a pilot study, administered a single dose of low-dose nivolumab, with or without an HBV vaccine, to 20 virally suppressed HBeAg-negative patients with chronic HBV infection. In virally suppressed patients with chronic HBV infection and low levels of HBsAg, ICIs treatment may increase the rate of HBsAg loss.

ASC22 (envafolimab) is a subcutaneously administered PD-L1 antibody that is used for treating advanced solid tumors. A phase IIb study revealed that administering a combination of ASC22 and NUCs once every 2 weeks for a total of 24 weeks reduced the levels of HBsAg.[17] Another phase Ib/IIa study revealed that administering a combination of VTP-300 (a therapeutic vaccine) and low-dose nivolumab (0.1 mg/kg) reduced the levels of HBsAg, with the most prominent reduction observed at HBsAg levels of <100 IU/mL at baseline.[18]

CONCLUSION

Chronic HBV infection results from the impairment of CD8+ T-cell function. The primary goal of chronic HBV infection treatment is to avoid of cirrhosis and HCC. HBsAg loss is associated with a low HCC risk and a relatively promising prognosis. Multiple strategies have been projected to achieve a durable viral control for HBV. Evidence suggests that combining ICIs with NUCs is a promising approach for achieving HBsAg loss, particularly in patients with low HBsAg levels.

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