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New treatments to reach functional cure: Rationale and challenges for emerging immune-based therapies

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A B S T R A C T

The landscape for chronic HBV therapy is rapidly evolving. The latest generation of antiviral drugs provide robust virus suppression with a high barrier to resistance that facilitates long-term treatment. However, low rates of HBsAg loss demonstrate that additional strategies are needed to consistency achieve a functional cure. The immune system can clear HBV and establish long-term control over the virus. Sufficiently boosting HBV immunity in chronic patients has been very difficult due to immune exhaustion, immune dysregulation, and inhibitory pathways suppressing the immune response. Therapeutic vaccines employing new technology, vectors and new immunomodulatory drugs that can elicit direct antiviral effects and cancel inhibitory mechanism may be able to overcome exhaustion. This review will discuss the justification for immunotherapy, lessons from previous trials and new vaccines/drugs in early stage clinical trials. The challenges of correlating immune responses induced by these drugs to clinical efficacy will also be addressed.

Introduction

The ability of Hepatitis B virus (HBV) to establish the long-lived extrachromosomal cccDNA replication template, the excessive production of viral antigens and the immune-suppressive environment of the liver have posed significant therapeutic challenges. However, it is clearly established that the immune response during acute HBV infection is able to overcome the suppressive environment and eliminate HBV from hepatocytes without complete destruction of the liver. This requires a coordinated immune response that relies on an effective CD4 T cell, CD8 T cell and B cell response resulting primarily in non-cytolytic HBV clearance and production of anti-HBV antibodies as a serological marker of long-term HBV control [1].

The contrasts between patients that resolve acute HBV infection and those with chronic infection have been extensively studied. In general, these data support the dogmatic statement that resolved patients display a broad and robust HBV-specific T cell response while T cells in chronic HBV patients display reduced frequencies and are functionally hyporesponsive. The challenge has been to understand why the immune response has failed in chronic HBV, what maintains the hyporesponsive state, and whether it is possible to sufficiently restore HBV-specific immunity in chronic patients to achieve viral clearance and long-term control. At least some of these obstacles have been identified. We have a better understanding of inhibitory receptor expression on T cells [2], active elimination of HBV-specific T cells [3,4], potential defects in T cell priming by dendritic cells [5], metabolic suppression of immunity [6–8], dampening responses through regulatory T cells [9] and the immunosuppressive liver environment [10].

New immune-based therapies are beginning to build on this knowledge to improve potency of T cell targeted therapies such as vaccine potency and/or checkpoint blockade. Other strategies are focused on modulating the intrahepatic environment with drugs targeting innate immune cells to achieve localized production of antiviral and inflammatory cytokines. However, the history of immune-based therapies in chronic HBV infection has demonstrated the challenges that we face. In addition, immune based strategies will have to contend with the extraordinary high safety bar set by current nucleoside analogues.

This review will cover the primary areas of immunomodulation currently being tested in clinical trials. I will attempt to summarize background data and previous attempts that have led us to the

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current state of HBV immunotherapy. A majority of the focus will be on human immunity but some animal models have been instrumental to our understanding of pathogenesis and resolution and will thus be referenced. The final section of the review will address the difficulty of determining if a therapy is immunologically effective and whether this correlates with clinical efficacy.

Justification for immune control in chronic HBV

Immune control of HBV replication has been demonstrated in every potential model of HBV infection, from in vitro co-culture with T cells to evidence from chronic HBV patients. IFN-γ and TNF-α produced by HBV-specific T cells in co-culture with HBV producing hepatocyte-like cells results in a reduction in viral replication [11]. Transfer of HBV-specific T cells into HBV-transgenic mice ablates HBV replication in the liver of these mice [12]. Intrahepatic infiltration of IFN-γ producing T cells in acutely infected chimpanzees, where virtually 100% of hepatocytes are infected, leads to a non-cytolytic clearance of HBV whereas depletion of T cells leads to persistent infection [13–15]. Data from chronic HBV patients undergoing bone-marrow transplant from healthy immune donors can lead to clearance of chronic HBV infection [16–18]. Case reports demonstrate that a chronically HBV infected liver, transplanted into an immune recipient, can lead to clearance of the chronic infection [19,20]. All of these examples demonstrate the immune systems' ability to control HBV replication, many of them highlighting the importance of the HBV-specific T cell response.

The human data in bone marrow transplant or liver transplant patients provide evidence of the ability to clear chronic HBV infection by reconstituting the immune response but are extraordinary cases. So, what is the evidence that the immune response in chronic HBV patients is contributing to control of HBV during chronic infection, where the immune system has repeatedly been demonstrated to be weak? In fact, there are a small percentage of patients who do clear HBV, measured by a loss of HBsAg from the circulation. One study has investigated the antiviral T cell response in these patients compared to those with ongoing chronic infection and found significantly increased T cell responses in patients who lose HBsAg [21]. However, because it was cross-sectional, it is not possible to determine if the increased HBV-specific T cell frequency was the cause or result of HBsAg loss. In addition, data from liver biopsies has demonstrated that increased T cell frequency correlates with better control of viral replication and less liver inflammation [22]. Both studies provide evidence that increasing T cell immunity correlates with control of HBV replication.

Additional evidence from chronic, and in some cases resolved, HBV patients supporting ongoing immune control is observed in patients receiving immune-suppressive therapy. The relative risk of these classes of drug were recently reviewed and published by the American Gastrological Association [23]. Drugs with the highest risk of HBV reactivation were Corticosteroids and B cell depleting agents. Corticosteroids, used to treat inflammatory diseases, have long been known exacerbate HBV pathology. Steroids suppress antiviral immunity and bind to responsive elements on the HBV genome, enhancing HBV transcription, leading to HBV reactivation. B cell depleting therapeutic antibodies used in lymphoma treatment carries the highest risk of HBV reactivation. Up to 60% of chronic HBV patients have been show to experience HBV reactivation following B cell depletion. Even patients with resolved HBV infection (HBsAg negative, anti-HBc positive) are at risk of reactivation when B cell immunity is ablated. Furthermore, anti-TNF-α therapies, which are increasingly used for inflammatory diseases like colitis and rheumatoid arthritis, are associated with HBV reactivation. Thus, even in chronic HBV patients, where the immune response is considered weak and dysfunctional, there is ongoing immune control. The mechanisms for this control still require better definition but it is reasonable to hypothesize that further enhancing existing immunity in chronic HBV patients holds potential for successful immunotherapy.

Targeting adaptive immunity

Therapeutic vaccine trials

Adaptive immunity has been the primary focus of immune-based strategies, given that T cells are the primary effectors mediating clearance of infected hepatocytes and anti-HBs antibodies define disease resolution. A majority of that effort has centered on therapeutic vaccination. Therapeutic vaccination, unlike prophylactic vaccination in healthy individuals, tries to boost HBV-specific immunity in the context of an ongoing chronic infection. The immune system in chronic HBV patients is persistently challenged with virions and HBV antigens in both the blood and liver. This persistent exposure to viral antigens is likely the primary driver of immune exhaustion, and poses a significant obstacle to overcome. The amount of antigen in the blood and liver, up to 1 mg/ml HBsAg (~200,000 IU/ml) in the serum, can easily overwhelm the amount of antigen delivered in vaccines [24,25]. Therefore, vaccination strategies have to deliver antigen in such a way as to redirect the immune system to the vaccine and associated lymphoid tissue and away from antigen in the blood and liver to facilitate priming (Fig. 1) [26].

To date, there have been numerous therapeutic vaccine attempts that have largely fallen into 2 categories 1) formulations of recombinant antigen or 2) DNA vaccination with a few additional unique approaches. A list of vaccine trials is presented in Table 1. I have tried to be exhaustive, but may have missed some studies, and this does not account for unpublished data. There have been at least 18 published clinical trials attempting a therapeutic HBV vaccine. As evidenced by a lack of a licensed therapeutic vaccine for chronic HBV infection, none of the strategies have been consistently successful. However, these trials have been important to help us understand the challenge of boosting anti-HBV immunity and provided some evidence of what may be effective.

Therapeutic vaccination with recombinant antigens have tested repeated dosing with different compositions of the HBV PreS1, PreS2 and S antigens delivered with or without adjuvants [27–35]. These vaccines were relatively weak at inducing T cell immunity, which were mainly measured using low-resolution T cell proliferation assays. T cells could be detected during or shortly after vaccine regimens in some studies but rapidly waned during follow-up. It was demonstrated that adjuvanted HBsAg vaccines could induce robust anti-HBs seroconversion, without HBsAg loss, in chronic HBV patients [27]. Thus, these trials demonstrate that weak stimulation of T cell immunity, even in the presence of a significant anti-HBs response, is not sufficient to overcome the threshold needed to induce clearance of HBV. The disconnect between vaccine response and virus control is an important topic that will be discussed below.

Because of the key role T cells play in HBV control, numerous studies attempted DNA vaccination, which primarily induces CD4 and CD8 T cell immunity [36–41]. Similar to trials with recombinant antigen, DNA vaccination strategies have used repeated intramuscular injections. In many of these trials, the vaccine was able to induce HBV-specific T cell immunity measured by proliferation and Elispot assays. However, the focussed effort to boost T cell immunity using DNA vaccines did not increase HBsAg loss in chronic HBV patients.