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Mini Review

Therapeutic Options for Chronic Hepatitis B: Present Status and Future Projections

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Abstract

Chronic hepatitis B virus (HBV) infection represents pathological conditions that is induced by HBV, but the nature and course of the disease is determined as outcomes of host/HBV interactions. In fact, HBV is a non-cytopathic virus and no toxin or other invasive properties. Although the cellular and molecular mechanisms underlying liver diseases by HBV are not yet completely understood, dominant roles of host immunity are considered as important determinants underlying HBV-related pathological processes. These concepts are supported by the fact that all anti-HBV drugs are although able to induce HBV negativity in the serum, but they cannot eradicate all forms of HBV. Even, anti-viral drugs cannot regulate the expressions of integrated form of HBV, cccDNA. Although several drugs have been developed for treating chronic HBV-infected subjects, considerable reservations have been prevailing about the safety, anti-viral & liver-protecting effects, and anti-fibrotic & anti-cancer potentials of these drugs. In this perspective, there is a pressing need to develop new and innovative therapy for chronic HBV-infected subjects. Immune therapy seems to be such an alternative, however, there has been no consensus about the design and formula of immune therapy for chronic HBV. In this article, we have attempted to provide comprehensive accounts about ongoing anti-HBV therapy and kinetics of evolving therapies.

Keywords: Chronic Hepatitis B; Drug Therapy; Immune Therapy; Vaccine Therapy; NASVAC

Abbreviations

HBV: Hepatitis B Virus; CHB: Chronic Hepatitis B; LC: Cirrhosis of Liver; HCC: Hepatocellular Carcinoma; HBsAg: Hepatitis B Surface Antigen; HBcAg: Hepatitis B Core Antigen; HBxAg: Hepatitis B X Antigen; DAA: Direct Acting Antiviral; IFN: Interferon; NASVAC: HBsAg/HBcAg-Based Vaccine

Diverse Pathology Induced by HBV

Hepatitis B virus (HBV) infection is global in nature. About 2 billion people of the world have been infected by HBV at some point of their life. Among them, about 240 million are regarded as chronic HBV carriers as they express both HBV DNA and hepatitis B surface antigen (HBsAg). Among these chronic HBV carriers, considerable numbers of these patients would develop liver damage (chronic hepatitis B, CHB) and all patients with CHB are prone to develop cirrhosis of liver (LC) and hepatocellular carcinoma (HCC). All patients with chronic HBV infection also remain in risk of developing liver failure due to various factors [1-3]. Thus, development of efficient therapy for these vast millions of people is a challenge of our time.

From the point of public health discipline, all chronic HBV carriers are living, and permanent reservoir of HBV and they transmit HBV to normal and apparently health persons who have not been protected by prophylactic hepatitis B vaccine. Due to these realities, millions of new HBV infection take place each year around the world [4]. Thus, HBV infection represents a disease entity that would provide major impact on health care delivery system indicating that proper therapeutic options should be developed for millions of chronic HBV-infected patients so that any further surge of HBV transmission may be checked efficiently. Even if this can be achieved, it may take several decades to contain HBV infection.

Management of HBV infection by anti-viral drugs

As several million people of the world have been suffering from CHB and its complications like LC and HCC with about one million HBV-related death each year, several drugs have been developed for treating these patients. From early 1980s, interferon (IFN) has been used in CHB patients for control of HBV replication and containment of liver damages. In course of time, pegylated form of IFN became available so that the therapeutic regimen become more patient-friendlier and less expensive [5,6]. In the meantime, a group of drugs capable of directly inhibiting HBV replication emerged as directly acting anti-viral (DAA) drugs and extensively used in CHB patients [7-9]. Subsequently, DAAs were used in patients with LC. A comprehensive assessment of the utility of these drugs would highlight the following points [10,11]:

1. DAAs are capable of blocking HBV replication, but they are not efficient to contain cccDNA that remain un integrated form in the hepatocytes of HBV-infected patients.
2. Thus, HBV DNA negativity induced by DAA merely represents disappearance of HBV DNA from blood, not from the liver. In fact, cccDNA in the liver may act as a template for HBV replication and may enter in replication cycle even long after HBV become negative in the blood.
3. Cessation of DAA is not an optimistic choice and these drugs do not have any finite usage.
4. Although HBV DNA negativity as well as seronegative or seroconversion of hepatitis B e antigen may be achieved by DAA therapy, these virological or immunological conversion is not related to containment of liver damages or progression to LC and HCC.
5. The immune modulatory capacity of DAA is not enough to alter immune status of CHB patients.

Concept of new and innovative therapy for CHB

Out of 2 billion HBV-infected subjects, chronic HBV carrier state develops in 240 million and less than 100 million develop CHB. Although the mechanisms underlying these events have not been clarified in detail, it is assumed that different stages of HBV infection and diverse levels of liver damages by HBV represents a factor of host-immunity-related fallacies. It is to be mentioned that millions of HBV-infected patients have high HBV replication but no liver damage. On the contrary, many patients with HBV infection develops CHB, LC and HCC even with very low levels or no detectable levels of HBV DNA [12-14]. However, host immunity, a factor of host/HBV interaction seems to be a regulator of determinant of HBV-related liver diseases. Also, the CHB patients that respond to IFN or DAA therapy also exhibit restoration of different parameters of host immunity [15,16]. These factors pointed towards immune therapy of CHB patients, however, the design of immune therapy became a matter of decade-long research and clinical trials.

Initially, CHB patients were treated with polyclonal immune modulators like cytokines, growth factors and various immune modulating agents. Also, cells of innate immunity were accentuated by various means. However, the final outcome of a therapeutic utility of these immune interventions is yet to be confirmed in clinics [17-26].

In mid 1990s, treatment of CHB patents by HBV antigen-specific immune modulators became a topic in clinical hepatology. Several investigators used prophylactic vaccine containing HBsAg and its variants to immunized CHB patients with various protocols. It appeared that prophylactic vaccines may have some sorts of antiviral and immunological properties, however, due to lack of term follow up, the utility of HBsAg-based vaccine therapy remained a controversial issue. Also, the mechanisms underlying response versus non-response of HBsAg-based immune therapy was not explored in detail. In addition to HBsAg-based immune therapy, various additional therapy based on HBsAg-based vaccine was accomplished. HBsAg was used as combination therapy with DAA, HBsAg/anti-HBs complex vaccine was used in China. DNA vaccine expressing HBsAg was also accomplished in different countries. HBsAg-based cellular vaccine was also tried in CHB patients. Finally, it seems that the nature and properties of therapeutic vaccine should be different from HBsAg-based prophylactic vaccine [27-38].

Different studies in CHB patients exhibited that hepatitis B core antigen (HBcAg) is an important regulator of pathological condition of CHB patients. Also, it became evident that so-called CD8-positive cytotoxic T cells (CTL) are not committed to destroy infected cells, rather, there is another system of control of viral replication and liver protection by a non-cytopathic manner, possibly via proinflammatory mediator produced by CTLs. This led to use HBcAg as a vaccine component for treatment of CHB patients. Some investigators used HBcAg as an adjuvant and pulsed with regulating immunocytes and used to treat CHB patients. On the other hand, others used HBcAg along with HBsAg and HBxAg in yeast formulation to treat CHB. It is hard to comment about the efficacy of these approaches as different investigators used different protocol as well as different subjects [39,40].

We have used a mixture of HBsAg and HBcAg (called NASVAC, Center for Genetic Engineering and Biotechnology, Havana, Cuba) to treat CHB patients via nasal and injection route. The outcome

of the Phase I/II/III trials are inspiring and NASVAC seems to be a better therapeutic choice than pegylated IFN in treatment naïve patients with CHB [41-44].

Concluding Remarks

HBV acts like a terrorist virus, although smallest among human viruses, integrated into host genome and may enter in replication cycle due to multiple factors, some of which is known, whereas, others are still unknown. Although immune therapy seems to be safe and a promising therapeutic choice, still the workable design has not been optimized. Also, mechanisms underlying response to immune therapy versus non-response remains to be elucidated.

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