

ABSTRACT

Chronic hepatitis B virus (HBV) carrier state is not a single disease entity, rather it covers a wide variety of pathological processes starting from minimal liver damage with variable levels of HBV replication as well as with potentials to develop life-threatening complications of HBV like liver cirrhosis, liver failure and hepatocellular carcinoma. These patients are not recommended for therapy because there are no effective therapeutic regimens for them, but they should be treated because they are living and permanent reservoirs of HBV and may also develop intractable liver damages. Thus, there is a need to develop alternative and new evidence-based therapy for these patients as well as other groups of patients. The authors of this manuscript have been working for more than a decade to develop immunotherapy for these patients. This submission will provide a comprehensive discussion about the reality of this problem and the therapeutic direction for them.

After the discovery of hepatitis B virus (HBV) in 1970s, significant progresses has been made about virology, epidemiology, natural course, pathogenesis, prevention and therapy of HBV and its complications.¹⁻³ Potent vaccines are now commercially available and several groups of drugs with antiviral and immune modulatory capabilities are available. These combined developments of basic and pharmacological aspects have contained further progress of HBV to some extent. However, effective and satisfactory regimens of management and therapy that would control further progression of HBV and manage HBV-related pathogenesis and complications are yet to be surfaced. One of the major obstacles to win over HBV is the existence of millions of so called "Chronic hepatitis B carriers", the entity and definition of which is difficult to ascertain and treatment and management of which remains in considerable gray zone.

Prior to initiating a discussion about present status of therapy and management of chronic hepatitis B virus carriers, it is of utmost importance to have more insight about the definition and entity of these patients. In general term, patients expressing hepatitis B (HBV) DNA and hepatitis B surface antigen (HBsAg) without evidence of elevated alanine aminotransferase (ALT) are regarded as chronic hepatitis B virus carriers.⁴⁻⁷ There are several hundred million chronic HBV carriers in the global context. However, there are inherent limitations of these definitions and their clinical implications. A group of patients may be diagnosed as chronic HBV carriers

because the virological, biochemical and immunological markers of them may mimic inactive or healthy HBV carriers. They may appear to have sustained normalized of ALT with a natural seronegativity of hepatitis B e antigen (HBeAg) or seroconversion of HBeAg to anti-HBe and/or seronegativity of hepatitis B surface antigen (HBsAg) and seroconversion of HBsAg to anti-HBs. On the other hand, there may be another group of patients, who will also be several hundred millions, who express ALT within normal limit at one point of assessment with HBV DNA and/or HBsAg and variable levels of HBeAg, anti-HBe, HBsAg, and anti-HBs would be regarded as chronic HBV carrier in clinical practice. The management strategy of patients with real inactive carrier state versus those with apparent inactive HBV carrier state assessed by measuring HBV-related markers at one point of clinical course should differ considerably.¹⁻⁷

Almost all international and national liver organizations do not recommend any specific treatment measures for true inactive HBV carriers who have attained sustained control of HBV and liver damage for prolonged period of time (8-10). However, these patients are living and permanent reservoirs of HBV and in fact they are also responsible for transmission of HBV to healthy individuals. In spite of these facts, there is no recommendation for treatment of these patients, because there is no effective drug for them. These patients are in immune tolerance phase and harbor small amount of replicative HBV DNA and without any noticeable evidences of adequate host immunity to HBV and its products. The purpose of therapy would be to make them free of HBV. However, the available antiviral drugs are not effective to eradicate HBV in these patients. It should be clear that therapy is not recommended by AASLD, EASL, APASL, and other regional and national liver organizations because of the facts that there is no drug effective for these patients.⁸⁻¹⁰ And, it is not true that treatment is not needed for these patients. HBV is a very complex virus and once it enters into the human body, it remains in some form in those patients for decades and possibly for life even after negativity of all HBV-related markers including HBV DNA. Again, we must remember the limitations of assessing HBV DNA and HBV-related markers in real life situation. These are usually accomplished in sera in almost all patients and HBV status in the liver i.e. presence of HBV DNA and HBV-related antigens, remain unknown. Also, a matter of serious consideration is the fact that HBV DNA replicates in the liver. There may be cccDNA in the liver in absence of HBV DNA and HBsAg negativity in the sera, however,

these patients may still allow HBV replication due to alteration of life style, usage of immune suppressed drugs and other medications, and for several unknown factors those could not be elucidated properly till now. Of more importance is the reality of managing these patients in resource-constrained and developing countries of the world that harbor most chronic HBV-infected patients and the utility of recommendations by AASLD, EASL, and APASL cannot be fully applied in these countries.^{11,12}

On the basis of these facts, the following points may be considered as hotspots regarding management of chronic HBV carrier:

1. A group of these patients represent inactive and healthy HBV carrier. They may allow active HBV replication, but do not exhibit evidences of liver damages.
2. A second group may be negative for HBV-related markers and ALT at the helm of an assay of a single time. However, that may merely represent a state of natural course of HBV in remission phase and that may be succeeded by exacerbation phase in near future.
3. In real life situation, a workable diagnosis of HBV carrier state is accomplished on the basis of retrieved data from sera, and the replicating site of HBV the liver remain mostly unattended by clinicians to assess chronic HBV carrier state.
4. The expression that “treatment is not required for chronic HBV carrier” represents grave flaws in Hepatology and related branches of medical science. Rather, it should be clearly mentioned that although treatment is required for these patients, that is not recommended because of lack of appropriate drug that would benefit these patients.

Next, it is of utmost importance to develop and design innovative and alternate therapy for these patients. And, that would provide insights regarding our role and those of others to develop alternate and evidence-based approach of drug development for containment of HBV and HBV-related diseases. As we mentioned, drugs are not recommended for these patients because there is no effective drug, but these patients may require therapy. It is natural query why antiviral drugs being so mighty are unable to control HBV and HBV-related complication in HBV-infected patients. There are several facts for these observations:

1. All antiviral drugs for HBV have not been developed depending on the life cycle and pathogenesis of HBV. Rather, the most of these drugs were developed to control retroviral infection and just modified to conform in HBV situation.
2. Accordingly, these drugs are capable of controlling or regulating replicative HBV satisfactorily and with vigor, but unable to control cccDNA and possibly extra-hepatic HBV DNA.

3. The immune modulation capacity of these drugs are neither appropriate in the context of quality or quantity. Some of these induce immune restoration in some patients as a secondary effect of HBV containment.

These facts indicate that some drug may be required to offer an effective therapy for chronic HBV carriers and immune-therapy became an area of development of innovative therapy for HBV-related pathologies.^{13,14} After the usage of antigen non-specific immune inducers in HBV-infected patients, HBV antigen-specific immune therapy has been initiated in these patients during the last two decades. HBsAg-based immune therapy was safe and effective initially but sustained control of HBV replication and containment of liver damages could not be accomplished with that approach and even various modifications of HBsAg-based immunity could not stand the test of time. With the understanding that HBcAg-specific immunity contain HBV replication and control liver damages and HBsAg-based immunity control HBV in the sera, a new therapeutic vaccine have been developed by our in-house studies and clinical trials¹⁵⁻¹⁸ and phase I/II/III clinical trials have been accomplished in patients with chronic hepatitis B (CHB) in Bangladesh. This HBsAg/HBcAg-based therapeutic vaccine is capable of inducing HBV-specific broad-based immunity and we are planning to use this therapeutic vaccine for treating chronic HBV carriers. The role of this therapeutic vaccine has been assessed in an animal model of HBV carrier state to see the feasibility of this therapeutic vaccine in asymptomatic, healthy and inactive HBV carriers. The data of trials in HBV transgenic mice, an animal model mimicking inactive and healthy HBV carrier is extremely exciting and it seems that this therapeutic vaccine may induce anti-HBs in HBV TM.^{19,20}

In conclusion, all HBV-infected subjects should be treated, because patients with prolonged suppression of HBV replication and controlling liver damages may develop HBV-related complications and also may transmit HBV to healthy and HBV uninfected subjects. The challenge is how to treat? The available antiviral drugs would not be effective and a complete dependence on the future trials with innovative immune therapeutic agents represent hopes for the time being. However, irrespective of these developments, all chronic HBV carriers should be properly followed up and the avenue of drug development for these patients should be prioritized.

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