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Progress Report

Chronic hepatitis B: Are we close to a cure?

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ABSTRACT

Approximately 300 million people worldwide are persistently infected with the hepatitis B virus and are at risk of developing hepatocellular carcinoma and liver cirrhosis, which can progress to end-stage liver disease. Despite the effectiveness of the current vaccination policy, the prevalence of the disease remains high, and the burden for health services is considerable. The currently available antiviral strategies are either poorly effective or only effective for non-curative suppression of viral replication. Recent efforts have been focused on improving the cure rate for chronic hepatitis B and developing strategies to eliminate infected cells.

Several approaches are under evaluation, and these include targeting the virus at different stages of its life cycle and boosting the antiviral immune response. This article reviews these latest approaches and comments on their feasibility and potential translation into clinical applications.

1. Introduction

Hepatitis B virus (HBV) infection is a major global health problem, despite the availability of effective vaccine prophylaxis. According to the latest World Health Organization (WHO) reports, an estimated 240–280 million people are chronic hepatitis B (CHB) carriers, among whom the disease occurs with a very high burden, as approximately 1 million people die every year from CHB-related disease [1,2].

Dramatic improvements in the efficacy of the treatment of chronic hepatitis C were made possible by the availability of highly potent direct antiviral agents, which created an expectation of similar results being achieved in chronic HBV.

Despite the availability of highly effective direct antiviral agents for HBV for the last 17 years, a cure cannot be achieved in most cases because of the peculiar features of this virus.

In fact, the viral life cycle of HBV involves the formation of particularly stable episomal minichromosomes, covalently closed circular DNA (cccDNA) molecules, which serve as a template for transcription and a reservoir for future replication cycles [3,4]. Furthermore, the HBV genome is able to integrate into the host genome, thus reinforcing viral antigen production and favouring HBV oncogenesis [5].

The inability to arrest this complex replicative machinery leads to the persistence of viral antigen production, which, in turn, progressively exacerbates the functional failure of the immune response; the immune response represents the most effective tool for viral control [6].

A CHB "cure" can be defined at different levels. Basically, the most desirable end point is the elimination of both the viraemia (HBV-DNA) and the viral surface antigen (HBsAg), followed by seroconversion to anti-HBsAg (anti-HBs) antibodies [7]. This condition is largely satisfactory because it is associated with a substantial improvement of outcomes and a reduced risk of developing complications, at least in non-cirrhotic patients [8–10]. A complete cure, however, would only be accomplished by elimination of cccDNA from infected hepatocytes, which represents definite viral eradication and ensures protection from the risk of reactivation in the case of immunosuppression [11] (Fig. 1).

However, both of these endpoints still represent a challenge because they are not adequately met by current therapies. Therefore, clinicians must rely on a surrogate but more realistic end point, which is the induction of sustained virological remission [1,12].

The current research aimed at designing new strategies for HBV "elimination" focuses on the following two main assumptions derived from the known mechanisms underlying viral persistence: (a) The need to target the virus directly and/or (b) the need to restore an effective immune response.

2. Current HBV therapies

Two different therapeutic approaches are currently available for patients with CHB: (1) a finite antiviral and immunomodulatory

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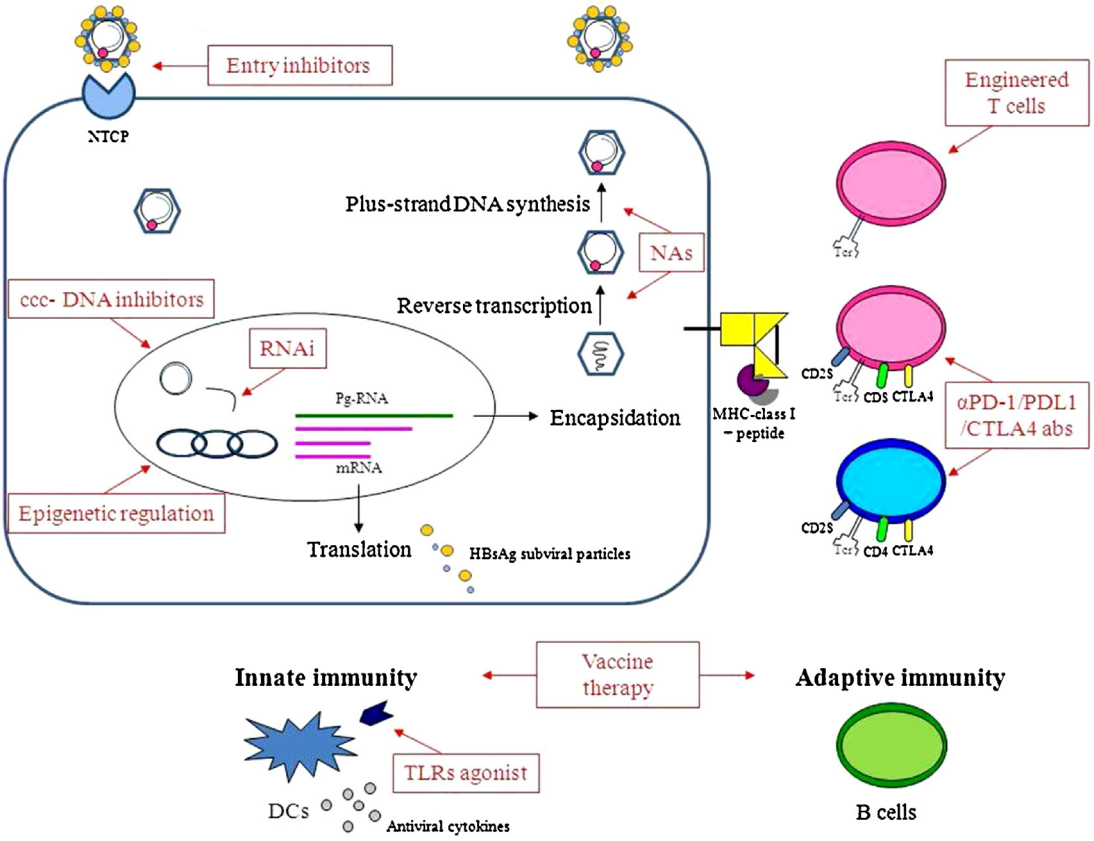

Fig. 1. Schematic representation of the potential curative approaches for chronic hepatitis B. NCTP, sodium taurocholate cotransporting polypeptide (HBV receptor); NAs, nucleos(t)ide analogues; DCs, dendritic cells; TLRs, Toll-Like Receptors; RNAi, RNA interference; TcR, T cell receptor.

treatment with interferon-α; and (2) an indefinite treatment with nucleos(t)ide analogues (NAs), which can successfully achieve non-curative suppression of viral replication [1] (Fig. 2).

Treatment with pegylated interferon-α (PEG-IFNα2a) can have a curative effect mediated by viral inhibition and an enhancement of the host immune response. Unfortunately, a curative effect of PEG-IFNα2a is observed in fewer than 10% of patients, regardless of HBeAg status [13,14].

A better definition of the factors that predict the response, such as HBsAg levels, viral genotypes, and HBeAg levels for the HBeAg-positive population, and validation of the stopping rules will most likely result in better selection of the patients to be treated, which, in turn, will lead to higher rates of treatment response [15]. However, these optimization attempts would lead to improved effectiveness of PEG-IFN therapy based on the exclusion of patients with unfavourable features; consequently, this strategy would not impact the overall cure rates for CHB.

Since the introduction of lamivudine in 1998, four other agents with progressively higher antiviral activity and a more efficient genetic barrier to drug resistance have been approved. These drugs successfully achieve satisfactory HBV DNA suppression rates, which are stably maintained with third-generation NAs (entecavir and tenofovir), at least based on the data acquired to date [16,17] (Fig. 2).

NAs inhibit HBV DNA synthesis via a competitive interaction with the natural substrates of the HBV polymerase; however, they do not interfere with cccDNA formation (Fig. 1). As a consequence, in most patients, HBV replication rebounds after antiviral therapy is discontinued.

Based on these findings, is it possible to achieve significant CHB cure rates with these agents? The currently available data would suggest otherwise: HBsAg seroclearance is considered a rare event during NA therapy; this event is observed in only 0.5–1% of all treated patients per year. The rate of decline of serum HBsAg levels is such that, according to mathematical models, a complete

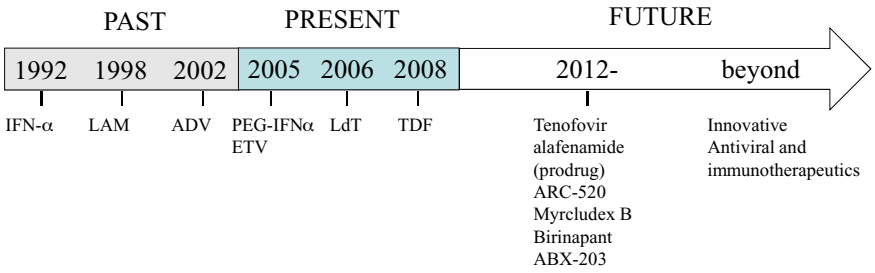

Fig. 2. Timeline of milestones in chronic hepatitis B treatment. The new drugs at a more advanced stage of development (phase III) are listed as "future". LAM, lamivudine; ADV, adefovir dipivoxil; ETV, entecavir; LdT, telbivudine; TDF, tenofovir disoproxil fumarate.