Review

Chronic hepatitis B: Immunological profile and current therapeutic vaccines in clinical trials

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Abstract

More than 250 million people worldwide are chronically infected with hepatitis B virus (CHB), and over half a million die each year due to CHB-associated liver complications such as cirrhosis and hepatocellular carcinoma. The translation of immunological knowledge about CHB into therapeutic strategies aiming to a sustainable hepatitis B virus (HBV) clearance has been challenging. In recent years, however, the understanding on the immune effectors required to overcome chronicity has notably increased thanks to preclinical and clinical research. Therapeutic vaccination may prove to be useful for treating CHB patients when coupled with current antiviral agents and other immunomodulatory strategies. This review summarizes current data and future perspectives on therapeutic vaccination. Other treatment alternatives that could be combined with vaccines for a complete cure from hepatitis B virus infection are also discussed.

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1. Introduction

Worldwide today more than 250 million people are chronically infected with the hepatitis B virus (HBV). Each year there is a growing number of deaths due to chronic HBV infection related diseases [1]. Almost a half of the world population lives in high HBV endemic areas, including many emerging countries of Africa and the Asian-Pacific region [2]. Although large campaigns of preventive hepatitis B vaccination have efficiently decreased the incidence of new infections for almost 30 years, chronically infected individuals are still the reservoir for viral spread.

Resolution of acute HBV infection is due to the induction of helper and cytotoxic T-cell response against viral proteins and the presence of HBV-envelope-specific antibodies. The quality of this immune response has been reported to be dependent on the age at the time of primary HBV infection and is known to influence the evolution towards chronic hepatitis B (CHB). In adults, self-limited infections generate an efficient anti-HBV response including T cells that secrete Th1 cytokines, which proliferate and lyse infected hepatocytes [3]. Hence, most of the acutely infected adults are able to efficiently control the virus.

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In contrast, a high percentage of infected neonates (90%) and children develop CHB. This age-dependent evolution of infection seems to be related with differences in the immune response quality during life rather than to the presence of an immature or "defective" immune system in newborns and infants [4]. In newborns a defective HBV-specific T-cells priming may occur leading to chronicity. It has been suggested that this might be due to in utero tolerization of the fetal immune system by maternal-derived HBeAg [5,7]. Although several treatments are available to control viral replication and avoid progressive liver tissue damage and the ensuing complications, there is still no complete cure for CHB. The use of standard and pegylated interferon-alpha (Peg-IFN-α) and nucleos(t)ide analogues (NA) which require a life-long treatment and many undesirable side effects have been linked to IFN-α and to nucleos(t)ide analogues (NUC) which require a life-long treatment [6]. Considering the lack of efficient treatments, there is a growing interest for new therapeutic approaches. This review will focus on therapeutic vaccines that are currently in clinical trials either alone or combined to existing drugs.

2. Chronic hepatitis B infection

The natural history of CHB infection can be divided into 5 main phases [5]:

– Starting with an "immune tolerant" phase, characterized by high viremia, hepatitis B "e" antigen positive (HBeAg(+) ), normal serum alanine aminotransferase (ALT), and minimal or no liver necro-inflammation. A low secretion of IL-10 and pro-inflammatory cytokines is observed at this stage, corresponding to slow or no fibrosis progression. This stage is referred to as a "training" phase for the immune system [7], and is typically seen in perinatal transmitted infections.

– The "immune clearance" phase begins with fluctuating serum levels of viral particles and ALT, evolving toward low or undetectable DNA values and to normal ALT (<30 IU/mL for men and <19 IU/mL for women). The initial fluctuations indicate the occurrence of intermittent hepatitis episodes, eventually leading to HBeAg seroconversion (the loss of HBeAg and the appearance of anti-HBe antibodies). Liver necro-inflammation levels could vary during this phase.

After HBeAg negativization, patients may progress directly toward HBeAg-negative chronic hepatitis or develop an inactive chronic carrier state for several years.

– HBeAg negative (HBeAg(−)) chronic hepatitis, also referred to as "reactivation phase", is characterized by moderate to high HBV DNA levels, the presence of HBeAg core and precore mutants, active necro-inflammation, elevated ALT, and progressive liver disease.

– The "non-replicative" or "inactive carrier" state is characterized by low viral replication (HBV DNA levels <2000 UI/mL), anti-HBe(+) status, normal ALT, and minimal liver lesions.

– The "occult infection": during this phase the hepatitis B markers hepatitis B surface antigen (HBsAg) and viral DNA are negative or undetectable in the serum, but HBV covalently closed circular (ccc) DNA and other replication-competent viral genomes persist in the liver [8].

These variable duration stages not always appear sequentially. The shift from one phase to another in any direction is possible. Two other theoretical phases were proposed for the complete HBV elimination: the clearance of cccDNA and the elimination of hepatic cells with integrated HBV DNA [5].

3. Chronic hepatitis B immunological profile

The harmonized action of both arms of the immune system is required to efficiently tackle viral infections. Unlike other viral infections, HBV induces a peculiar innate immune response: - it appears several (4–6) weeks after the infection, when HBV has reached a replication peak (10^6 copies/ml) [9] - it is characterized by a high production of IFN-γ instead of type I IFNs [10]. Additionally, HBV has a mechanism that interferes with the type I IFN antiviral effect [11,12]. Meanwhile, an elevated IFN-γ secretion precedes the detection of HBV-specific T-cells in acute patients, and correlates with a significant decrease in HBV replication. In self-limited infections, viral load is reduced by ~90% before liver damage can be detected, indicating that most of the virus is removed by non-cytopathic effectors, mainly IFN-γ and TNF-α [9]. During self-limited acute HBV infection an effective and multi-specific immune response is mounted, based on an early priming of vigorous CD4+ T-cell response. These Th1-oriented CD4+ T cells cooperate in the activation of CD8+ T cells, which migrate to the liver, secrete IFN-γ and TNF-α favoring the inflammatory process, the non-cytopathic antiviral mechanisms and ultimately kill infected cells. In addition, CD4+ T cells also help B cells in the development of a proper anti-HBV antibody response. Altogether, this conducts to successfully control the infection [9].

On the other hand, CHB infection is associated with the development of a weak and narrow specific T-cell response. The factors influencing the development of an inefficient antiviral immune response include: HLA-class II genetic profile, viral infecting dose, and age at the time of infection [3]. Indeed, the HBV-specific IFN-γ secreting CD8 T-cells are significantly reduced in the liver of CHB patients [13], and even more in highly viremic patients. In addition to the persistently high HBV DNA and the prolonged exposure to elevated amounts of viral antigens (HBsAg and HBeAg) characterizing chronic infection, the tolerogenic liver environment facilitates the promotion of many exhaustion mechanisms. Intra-hepatic priming that imposes a Bim<sup>high</sup> pro-apoptotic phenotype on T cells, as well as the increased expression of co-inhibitory signals from liver resident cells, impairs their effector functions [14]. After years of chronic infection, the HBV-specific T-cells are deleted or functionally exhausted. The remaining HBV-specific T-cells express inhibitory molecules such as Programmed cell death 1 (PD-1), Cytotoxic T lymphocyte antigen-4 (CTLA-4), Lymphocyte-activation protein 3 (LAG-3), 2B4 (CD224), Signaling lymphocyte-activation molecule (SLAM) and T-cell immunoglobulin and mucin domain containing molecule-3 (TIM-3), and are deficient in proliferation and cytokine production [3].

Although the HBV-specific CD8+ T-cells are not completely absent in CHB patients, epitope hierarchy is altered in proportion to viral load level. Even though a multi-specific CTL response distinguishes acute hepatitis, an epitope-specific CD8+ T-cell hierarchy is established. CD8+ T-cell response to the HLA-A2-restricted epitope Hbc18-27 is dominant; followed by the response to polymeric epitope (455–463). On the contrary, the HBsAg epitopes are subdominant. On the other hand, in persistent infection this hierarchy dramatically changes, where CD8+ T-cell response to envelope epitope (183–191) is always dominant [15,16].

Today, the mechanisms behind T-cell hypo-responsiveness or tolerance to viral proteins in CHB infection are not fully elucidated. Many different immunological processes can take place at variable degrees, such as negative selection, ignorance, peripheral anergy, exhaustion, down-regulation of cell surface molecules, imbalances
in cytokine secretion, and impairment of antigen-presenting cell function. For the design of therapeutic vaccines that can overcome the tolerogenic environment, it is essential to study the extent to which each one of these factors contributes to hypo-responsiveness to individual viral proteins [17].

The role of T regulatory (Treg) and T helper 17 (Th17) cells in CHB infection has been studied in more detail in recent years. It has been demonstrated that the number of Treg cells in the peripheral blood, and more importantly in the liver, increases with CHB infection. There is evidence indicating that Treg down-regulates HBV-specific effector T-cell responses [18–21]. Additionally, Tregs control the recruitment of innate immune cells such as macrophages and dendritic cells toward the infected liver. In general, Treg cells hamper the development of an efficient immune response, delaying viral clearance [22].

Furthermore, in CHB carriers, B cells secreting high-affinity antibodies against the carrier’s own HBsAg are unable to clear the virus. The antibody response is quantitatively and/or qualitatively insufficient to overcome chronic infection [23]. Among the possible causes of the failure of an effective antibody response against HBV are the overwhelming amounts of circulating HBsAg, an inefficient T CD4+ helper function, and potential functional impairments in antigen presenting cells [15,24].

On the other hand, several studies analyzed the role of natural killer (NK) cells during CHB infection. In this context NK cells display changes in proportion, phenotype and/or function that differ among studies. The NK cell variations are shown in many aspects: [1] in immune-activated CHB patients a reduced percentage of liver and peripheral NK cells is observed, with or without changes in their subsets; [2] altered expressions of activating or inhibitory receptors; [3] up-regulation of inhibitory molecules such as TIM-3; [4] enhanced cytolytic function, linked to increased liver injury; [5] its inhibitory role on adaptive immunity by killing activated CD8+ T and T follicular helper cells; and [6] impaired cytokine secretion such as IFN-γ and TNF-α. Studies indicate that while the anti-viral cytokine secretion of NK cells is impaired during CHB, the cytotoxic function remains intact or even increased. However, a partial restoration of NK cell numbers, cytokine production, and inhibitory receptor expression has been achieved after viral load reduction by an antiviral treatment. The inefficient activation of antiviral functions of NK has been related to the defects of dendritic cells in CHB, and also to the inhibitory effect of IL-10 secreted by Kupffer cells [25,26].

4. Therapeutic vaccines in clinical trials: Is the recovery of HBV-specific T-cell functions feasible?

The dichotomy of the specific immune response elicited in self-limited HBV versus the chronic infection makes it possible to hypothesize that the restoration of anti-viral immunity in chronically infected patients could lead to disease “cure”. There is evidence supporting the rationality of using immune-therapy for CHB treatment. The spontaneous resolution of CHB is reported in 5–10% of the patients. Perhaps the most important proof of this concept comes from graft experiments using a healthy immune system donor, containing HBV–primed cellular and humoral immunity. The resolution of chronic infection and HBsAg clearance in the recipient is induced on transferring these cells [15]. Moreover, the association of IFN-α therapy with the highest rates of HBeAg and HBsAg seroconversion highlights the relevance of immune modulation on HBV clearance [6]. However, antiviral therapy induces only a limited restoration of T-cell functions. A transient improvement of CD4+ and CD8+ T-cell responses induced by Lamivudine treatment in HBeAg(+) patients has been reported [9]. Recent studies in NUC-treated active CHB patients with the sustained suppression of viral replication indicate that despite a gradual and persistent recovery of HBV-specific T-cell functions in line with HBsAg reduction, this restoration remains frequently incomplete, even when HBeAg seroconversion is reached [9,27]. These results have led to the idea of using other immunostimulatory therapies, such as therapeutic vaccines, taking advantage of the partial restoration in T-cell immunity induced by the previous antiviral treatment. The strategy of combining different treatments to promote optimal immune stimulation in the context of CHB infection is now being studied.

Therapeutic vaccines are aimed to induce a functionally efficient anti-viral immune response overcoming the established HBV-specific T-cell exhaustion. Several strategies have been evaluated thus far in clinical trials with discouraging results [28,29]. New vaccine developments that evolve as a second generation of HBV therapeutic candidates are now under clinical evaluation by different companies (Table 1). Some of them are discussed below, focusing on their results and challenges. The yeast-derived HBsAg immune-complex (YIC) vaccine is interesting because of its unusual approach. This candidate contains HBsAg and human anti-HBs immunoglobulins (HBIG) using alum as the adjuvant. The safety of YIC among healthy adults and CHB patients has been proven in phase I and phase IIa trials. A double-blind, placebo-controlled, phase IIb YIC clinical trial reported therapeutic efficacy in CHB patients [30]. However, data published on a phase III trial gave unsatisfactory results [31]. In that study, twelve doses of YIC or alum alone, as the placebo, were randomly administered to 450 CHB patients who were followed for 24 weeks after ending the immunization schedule. HBeAg seroconversion was considered as the primary endpoint. The decrease in viral load, the improvement of liver function, and histological features were measured as secondary endpoints.

The effect on viral load and liver function was similar in both groups. In general, these results demonstrated that the administration of twelve doses of YIC reduces its efficacy due to immune exhaustion. An interesting result obtained from this for further studies is that the placebo group receiving multiple injections of alum alone showed a therapeutic effect, suggesting that alum administration could stimulate the beneficial inflammatory and innate immune responses. Both conclusions were later corroborated in mice experiments [32]. The experience from this first phase III trial with the YIC vaccine will help optimize immunization strategies for future studies.

The results of another vaccine candidate, GS-4774, were recently reported at the end of a randomized phase II study [33]. GS-4774 is based on heat-inactivated Saccharomyces cerevisiae yeast expressing HBsAg, the hepatitis B core antigen (HBcAg), and the hepatitis B X antigen. The fusion protein expressed uses sequences from the four main HBV genotypes worldwide. This candidate uses the natural adjuvant properties of the yeast component, potentially enabling the development of innate and T-cell responses. GS-4774 was evaluated in a phase I trial in healthy volunteers who received weekly or monthly subcutaneous (s.c.) injections (NCT01779505). The trial demonstrated that GS-4774 was safe and elicited HBV-specific T-cell responses in 88% of the individuals [34]. The phase II study recruited 178 CHB patients who were virally suppressed with approved HBV oral antiviral (OAV) drugs for ≥1 year (NCT01943799) [33]. The patients were randomized (1:2:2:2) to continue on OAV alone or receiving OAV plus GS-4774, using 2, 10, or 40 yeast units s.c every 4 weeks until week 20. All patients remained under the OAV treatment until the end of the trial at week 48. Efficacy was measured by the decline in the serum HBsAg from the baseline until week 24. In this phase II trial, how-
ever, all groups showed similar mean decline of HBsAg from the baseline to week 24 or 48. It was concluded that GS-4774 treatment did not show any clinical benefit, although its safety was demonstrated. In our opinion, the failure of this trial has to do with the efficacy endpoints and also with the decision to maintain the OAV treatment after the end of the vaccination. It is known that a significant decline or clearance of HBsAg is the golden endpoint for any CHB treatment [28]. A low percentage (<10%) of patients, however, reached this goal and in most cases this is obtained after many years with the use of a successful therapy [35,36]. In the GS-4774 study the HBsAg decline was measured only four weeks after the end of vaccine administration. Additionally, the continuous suppression of the viral load, due to the ongoing OAV treatment occurred until week 48. This could prevent the detection of an effect of the vaccine-induced immune response on HBsAg production. Evaluation of GS-4774 in different CHB patient populations and exploring several combinations is under way to elucidate its potential therapeutic effect [33].

The DV-601 candidate is a treatment approach that combines the HBsAg and HBeAg with the ISCOMATRIX® adjuvant [37]. After ending two phase I trials, DV-601 demonstrated its safety and immunogenicity [38,39]. The first study recruited 20 healthy volunteers and the second, a phase I b trial, recruited 14 CHB patients (NCT01023230). The study evaluated a treatment using six injections of DV-601 combined with Entecavir in an open-label, dose-escalating trial. Preliminary results showed that DV-601 was safe, well tolerated and elicited immune responses at all dose levels. Two patients out of eight developed antibodies against HBeAg and four out of fourteen developed antibodies against HBsAg. Virological responses (HBV DNA reduction) were observed at all dose levels. Additional data [38], showed the development of an HBV-specific lymphoproliferative response in all patients. Furthermore, an Hbc-specific IFN-γ T-cell response was detected in two out of six HBeAg(+) patients who received the highest dose of DV-601. Although phase I trials were completed a few years ago, the results have not yet been published in peer-reviewed journals neither larger studies are ongoing [40].

Another candidate, called HeberNasvac®, recently completed a phase III clinical trial in treatment-naïve CHB patients with successful results [41]. HeberNasvac® is composed of a combination of the HBsAg and the HBeAg [42]. Four clinical trials have been completed thus far with this vaccine candidate. A phase I trial was carried out in 18 healthy volunteers demonstrating the safety and tolerability of HeberNasvac® [43]. Subsequent clinical trials in chronic patients confirmed its safety and showed that the vaccine enhances viral control [41,44]. The phase III is a randomized, open-label, Peg-IFN treatment controlled trial, carried out in 160 treatment-naïve CHB patients (NCT01374308). The vaccine was administered once every two weeks. Five intranasal doses were applied in the first cycle, followed by a second cycle of five additional vaccinations through both the nasal and s.c routes. A dose of 180 μg of Peg-IFN was s.c administered once a week, for 48 consecutive weeks in the control group. The obtained results confirmed the safety and higher tolerability of this vaccination strategy compared to Peg-IFN. Furthermore, a superior sustained reduction of the serum HBV DNA levels was observed in HeberNasvac® treated patients during treatment-free follow up. HeberNasvac® also exhibited higher percentage of ALT normalization and HBeAg seroconversion after 48 weeks of follow up [41, publication ongoing]. Based on clinical results of HeberNasvac®, registration and marketing authorization were granted by the Cuban Regulatory Authority at the end of 2015. Currently a phase IIb/III trial with HeberNasvac® is ongoing to assess its efficacy as an adjunct therapy to NUCs, for the control of HBV replication after ending the treatment with NUCs (NCT02249988).

The DNA-based vaccines have also been evaluated for CHB therapeutic vaccination purposes, with or without the NUC treatment. Despite encouraging preclinical results only weak clinical improvements were noted in phase I and II trials [45,46]. The failure of these trials may be linked to the treated patient population, the form of delivery of the DNA vaccine and the very rigid clinical endpoints defined [47,48]. Currently, a new candidate using this technology is in phase I clinical trial (NCT02431312). INO-1800 is a mixture of recombinant DNA vaccines that encode the HBsAg and the consensus sequence of the HbcAg. Potent specific T-cell and antibody responses have been induced in preclinical studies with this candidate. The vaccine also elicited strong cytotoxic T-cell responses that were not associated with significant liver damage [49]. The ongoing phase I is a randomized, open-label, active-controlled, dose-escalation trial to evaluate the safety and immunogenicity of INO-1800 alone or combined with INO-9112 (DNA plasmid encoding human IL-12). Both plasmids are delivered intramuscularly by electroporation. The study was designed for 126 Entecavir- and/or Tenofovir-treated CHB patients [50].

Among the HBV-specific therapeutic vaccines previously tested in clinical trials only one was based on viral vectors, a poxvirus candidate [51]. TG1050 is a novel candidate consisting of a non-replicative adenovirus serotype 5 encoding a fusion protein formed by a truncated HBCAg, a modified HBV polymerase and two HBV envelope domains. During the pre-clinical evaluations, a potent, HBV multi-specific and long-lasting T-cell response was induced. Antiviral effects of TG1050, including seroconversion to HBsAg,
have also been shown in mice models [52]. This candidate is being tested in a randomized, double-blind, placebo-controlled, multi-cohort Phase I / I b study (NCT02428400). For all cohorts, CHB patients must be receiving antiviral treatment for at least two years, and their HBV infection must be well-controlled. This study explores the s.c administration of TG1050 in a single or a multiple-dose regimen and was designed to recruit 96 patients.

HepTcell (FP-02.2) is another vaccine candidate, formed by nine synthetic peptides derived from the most conserved domains of HBV and containing a high density of CD4+ and CD8+ T-cell epitopes restricted by multiple HLA alleles, thereby allowing the product to be used for any of the circulating HBV genotypes. HepTcell is currently in phase I clinical trial (NCT02496897)[53]. The trial is a randomized, double-blind, placebo-controlled, ascending-dose study. The safety and immunogenicity of HepTcell administered as an add-on therapy to Entecavir or Tenofovir is now being evaluated. Seventy-two HBeAg(−) subjects will receive low or high doses of the vaccine with/without the IC31® adjuvant, or will receive the placebo, or the adjuvant alone [54].

5. Combination therapies and novel therapeutic approaches

A functional cure for CHB, equivalent to resolved acute infection, is likely to come in the form of the combination of two or more therapies and will result in immune-clearance of the virus and a durable HBsAg loss with anti-HBs seroconversion [55]. In this sense, novel therapeutic strategies are being studied (Fig. 1) [56,57]. Some of these strategies could be combined with therapeutic vaccination to improve immune stimulation. The first developed vaccine combination therapies for CHB were based on the sequential or add-on administration with antiviral drugs, primarily Lamivudine [28,29]. This approach was supposed to improve the efficacy of therapeutic vaccination; however the selection of the patients, the timing of introduction of each therapy, and the nature of the vaccine formulation, strongly impacted in the outcome. Considering that current antiviral drugs constitute the first line of therapy in many countries, the introduction of a therapeutic vaccine should face up this scenario. Nowadays, combined therapy studies take advantage from the increased knowledge and include new drugs directed against viral targets different from HBV polymerase. In addition, studies of new nucleoside analogues for CHB treatment are under way [58].

Among approaches targeting the viral cycle, inhibiting viral replication by RNA interference (RNAi) is an interesting strategy. ARC-520, a small RNAi that target the HBV pre-genomic RNA, is now in a phase II clinical trial (NCT02604199) [56–58]. Another RNAi, ARB-1467, is currently in phase II trial as adjunct therapy to NUC (NCT02631096) [56,57]. The RNAi-based approaches showed good results inhibiting the HBsAg and HBeAg secretion in chimpanzees and during preliminary trials, however this strategy has some drawbacks regarding its efficient delivery to hepatocyte's cytoplasm and the induction of undesirable side
effects [56,57]. Another major problem could be the duration of the inhibition and its reduced effect in HBeAg(−) patients.

Nucleic acid polymers (NAPs) have been recently highlighted as promising antiviral agents for their unique ability to block the secretion of HBsAg from HBV-infected hepatocytes [59]. So far, two proof-of-concept trials (NCT02646163 and NCT02646189) were done in treatment-naive HBeAg(+) CHB patients using NAPs (REP 2055 and its derived REP 2139-Ca) [60]. Interestingly, the second study included an arm that transitioned from REP 2139-Ca monotherapy to a combined treatment with Peg-IFN α-2a or thymosin α-1. Both studies showed substantial reductions of serum HBsAg and HBV DNA, and the appearance of anti-HBs antibodies. However, NAP formulations exhibited some tolerability issues related with the i.v administration and the nature of the drug itself. These trials suggest that the NAP treatment can elicit important antiviral responses, which may improve the effect of immunotherapy. Other two clinical studies are ongoing (NCT02233075 and NCT02565719), the last exploring a NAP, NUC and Peg-IFN triple combination [60]. The potentialities of NAP combination with therapeutic vaccines should be evaluated in the future.

The viral entry inhibitors constitute another therapeutic approach currently being evaluated [56,57]. Among a group of compounds with this effect, Myrcludex-B, a synthetic lipopeptide derived from the HBV large protein, stand for is ability to inhibit cccDNA synthesis. Nowadays, Myrcludex-B is in phase II clinical trials in combination with Peg-IFN α-2a (NCT02657999 and NCT02885106).

Other alternatives are the inhibitors of the HBV nucleocapsid assembly [56,58]. Among them, NVR3-778 and GSL4 phase II trials are the most advanced. On the other hand, the approaches focused on host innate immune system stimulation are emerging as novel immunomodulators. GS-9620, a potent TLR-7 agonist is under phase II clinical trial (NCT02166047) in combination with OAV treatment [56,61].

Modulating inhibitory pathways is a strategy with promising results in cancer treatment. This approach can enhance HBV-specific T-cell effector functions (at least in vitro). Functional response to PD-1 and CTLA-4 blockade was better improved in vitro in HBeAg(−) than in HBeAg(+) CHB patients [62]. Reports of PD-1 blockade in HCV patients [63] and in patients with advanced liver cancer have shown that the safety of this approach can be managed [64].

In addition to novel drugs currently in the pipeline for CHB therapy, the publication of studies combining Peg-IFN with NUC [65–67] and the discontinuation of long lasting NUC treatment are in the spotlight. The Peg-IFN and NUC combination has the potential to exhibit clinical benefits compared with monotherapy, mainly in terms of HBsAg decline or seroclearance. Its application could be addressed using different strategies: de novo, ‘add-on’ or ‘switch to’. So far, it is unknown which of these are the most effective. Hence, until ongoing larger studies were finished, none of the combination approaches are approved for routine use [65]. The other current trend in treatment management is the potential safe discontinuation of long-term NUC therapy. Although the controversy in this field remains, some studies suggest that sustained virological remission could be feasible in an important proportion of patients after long-lasting treatment discontinuation [68–70].

6. Conclusion

Despite the increased knowledge obtained from previous HBV therapeutic vaccine candidates, none of these second-generation vaccine candidates has as yet demonstrated their efficacy. Although new vaccine developments include viral proteins, other than the envelope proteins, more potent Th1 adjuvants, and new vaccine vectors, the complex scenario of chronic hepatitis B infection is as yet an elusive challenge. In the future, researchers must carefully design appropriate immunization protocols focusing on primary efficacy endpoints and on the correct selection of recruited patients, considering parameters such as the natural history of the infection, the level of liver inflammation, HBeAg status, viral genotypes, the baseline level of HBsAg and the duration of previous treatments. Rational treatment combinations should also be explored. These points are crucial for the success of HBV therapeutic vaccination.

Conflict of interest

The authors declare that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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