



Towards a Functional Cure for Chronic HBV Infection: Progress, Setbacks, and New Hope

Editor's Pick

The pursuit of a functional cure for chronic hepatitis B (HBV) has been marked by periods of optimism, disappointment, and, more recently, renewed hope. In this compelling feature, Bertoletti examines the progress and setbacks that have shaped HBV cure research, from the early promise of RNA-targeting therapies to the recognition that hepatitis B surface antigen (HBsAg) reduction alone is insufficient to achieve sustained immune control. The article highlights emerging evidence that combination strategies involving small interfering RNA, peginterferon alfa, and therapeutic vaccination may substantially improve rates of HBsAg seroconversion and functional cure. Importantly, it underscores the growing appreciation of immune recovery, particularly HBV-specific B and T cell responses, as a critical determinant of treatment success. By exploring both the scientific rationale underpinning these advances and the challenges that remain, this timely review offers valuable insight into the next chapter of HBV therapy and the prospects for achieving a durable functional cure.

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Disclosure:

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INTRODUCTION

The quest for new therapies able to achieve a functional cure for chronic hepatitis B virus (HBV) infection has been characterised over the last 5 years by phases of hope followed by severe disillusionment.¹

It is well established that excellent drugs for the treatment of chronic HBV infection exist and have been in use for decades. Potent nucleoside and nucleotide analogues with a high barrier to resistance can be taken lifelong without severe side effects and achieve excellent control of HBV replication (undetectable serum HBV-DNA),

thereby reducing liver inflammation and the development of clinical complications of chronic hepatitis B (CHB), including liver cirrhosis and hepatocellular carcinoma.²

However, long-term treatment with nucleoside or nucleotide analogues rarely achieves a functional cure, defined as the sustained undetectable level of hepatitis B surface antigen (HBsAg) and HBV-DNA in serum in the absence of any treatment. This virological profile represents the ultimate goal of HBV therapy: it removes the social stigma of HBsAg positivity and carries clear clinical relevance, further lowering the risks of cirrhosis and hepatocellular carcinoma and allowing the safe discontinuation of nucleotide analogue therapy.

It is important to note, however, that functional cure does not reflect HBV elimination, which cannot be achieved in any HBV-infected individual. Patients who control HBV infection after acute illness still harbour a small number of hepatocytes containing the HBV minichromosome, known as covalently closed circular (cccDNA).

Furthermore, HBsAg, the sum of non-infectious subviral and whole viral particles composed of the three major proteins of the HBV envelope (PreS1/S2/S), is secreted not only by infected hepatocytes, but, particularly in adults with CHB, by hepatocytes carrying integrated HBV-DNA. Functional cure therefore represents a sustained reduction, rather than complete elimination, of the number of infected hepatocytes and/or those harbouring HBV-DNA integration.³ This can be achieved by compounds that directly target these hepatocytes, or by enhancing the immunological control of HBV, which is known to be defective in patients with CHB.⁴

TREATMENT PATHWAYS

This was the rationale behind two families of compounds, short interfering RNA (siRNA) and antisense oligonucleotides (ASO), designed to target HBV RNA and thereby reduce both HBV replication (by targeting the pregenomic RNA, the

template for HBV-DNA synthesis) and viral antigen production (principally HBsAg, by targeting the S mRNA originating from either cccDNA or integrated HBV-DNA). The possibility of delivering siRNA and ASO compounds selectively to hepatocytes via GalNAc conjugation made them even more attractive candidates.⁵

Initial data were promising. Treated patients experienced a steady decline in serum HBsAg; a reduction never observed with nucleotide analogue treatment, which targets HBV-DNA replication but not antigen production. It was quickly recognised, however, that HBsAg reduction reached a plateau after 16–20 weeks of treatment, and complete serum HBsAg clearance was never achieved with siRNA alone. Somewhat better results were obtained with the ASO bepirovirsen, a non-GalNAc-conjugated compound, in which HBsAg negativity was observed in approximately 9% of patients. However, this seroconversion occurred predominantly in patients with CHB who already had low HBsAg levels at treatment initiation.⁶

What these initial trials also revealed was that the rapid HBsAg reduction achieved with ASO or siRNA compounds was not accompanied by any meaningful recovery of HBV-specific immunity. A reversion of the dysfunctional HBs-specific T and B lymphocytes did not occur. Studies, in both animal models and patients with CHB, clearly showed that HBsAg reduction with siRNA alone does not lead to recovery of HBV-specific T or B cell function.^{7,8} Antigen reduction may yet prove useful in combination with therapeutic vaccines, but even here, the increased immunogenicity observed in siRNA-treated individuals treated with a therapeutic vaccine did not translate into higher rates of HBsAg seroconversion.^{8,9}

NEW DEVELOPMENTS

Recent data have, however, renewed genuine optimism. Results of the Phase 3 bepirovirsen clinical trial (24 weeks of treatment) show a 20% rate of functional cure (24 weeks after stopping all HBV

treatments) in non-cirrhotic CHB patients (HBsAg lower than 3,000 IU/ml).¹⁰ Even though the majority of patients responding have low levels of HBsAg between 1,000 to 3,000 IU/ml and the incidence of adverse events requiring dose interruption (16% of treated patients, mainly ALT elevation) call for stringent monitoring for the patients (at least every 2 weeks), this rate of functional cure achieved with a single compound is certainly remarkable.¹⁰

Also, the combination of siRNA with peginterferon alpha (Peg-IFN α) has been shown to yield HBsAg seroconversion rates of approximately 20–30%, not only in patients with non-cirrhotic CHB with low baseline HBsAg levels, but also in younger HBeAg-positive patients with CHB characterised by high HBsAg levels.^{11,12} Even more unexpected were the results obtained with siRNA plus Peg-IFN α in patients with CHB who had been vaccinated 2 years earlier with a therapeutic vaccine based on PreS1/S2/S antigens. Among patients who had responded to the vaccine by producing anti-HBs antibodies, the rate of HBsAg seroconversion reached 56% at the end of treatment, and a recent report of 37% of a functional cure 24 weeks after the interruption of every treatment.^{13,14} Taken together, these results demonstrate that a meaningful proportion of patients with non-cirrhotic CHB can achieve a functional cure when therapies that reduce HBsAg are combined with immunomodulatory agents.¹⁵

What mechanisms explain these results? Whether a toll-like receptor (TLR) agonist effect of bepirovirsen, in addition to its ability to suppress HBsAg, contributes to clinical efficacy is a plausible hypothesis and should be tested. It is important to remember that a non-GalNAc-conjugated ASO is, in essence, a single-stranded synthetic nucleic acid molecule that can be sensed not only by hepatocytes but also by myeloid cells (dendritic cells, Kupffer cells) present in the liver. Single-stranded nucleic acids can activate TLR7/8 (if they contain RNA-like features) or TLR9 (if they contain CpG features).

Similarly, we need to understand how Peg-IFN therapy increases the rate of

HBsAg seroconversion, and why does prior vaccination with a therapeutic HBV vaccine, which on its own was essentially ineffective (only one of 77 patients achieved HBsAg seroconversion), produces a striking 56% seroconversion rate when combined with siRNA and Peg-IFN α ?^{8,13}

The antiviral effects of Peg-IFN α are well established, but its immunomodulatory actions are likely equally important here. Natural killer cell activation has been proposed as one mechanism, but it is probably not the only one. IFN α induced during viral infection has been shown to potentiate both antiviral B cell and T cell responses.¹⁶ In CHB, while T cell dysfunction has received the most attention, B cell biology deserves equal scrutiny: HBs-specific B cell recovery has been demonstrated to correlate with seroconversion following Peg-IFN α therapy, and this arm of the immune response warrants much closer investigation.¹⁷

What seems clear is that antigen reduction alone, however dramatic, is insufficient to restore antiviral immunity. Rather, it appears to facilitate a synergistic interaction between the immune activation induced by the TLR-like function of ASO or Peg-IFN α with preexisting natural or vaccine-primed immunity.¹⁸ Understanding this interplay mechanistically is the key challenge ahead.

CONCLUSION

Crucially, future trials must move beyond virological markers alone. If immune recovery is driving these successes, immunological parameters such as T cell function, HBs-specific B cell responses, and antigen presenting cell activity must be systematically measured and used to guide treatment design.

Fortunately, newer whole-blood assay methods have substantially simplified immunological monitoring, making this feasible even in large multicentre studies.¹⁹

We are at the dawn of a new era in HBV treatment. Turning these initial, tantalising

results into a broadly effective therapy will require mechanistic clarity, smarter combination strategies, and a commitment

to studying the immune response with the same rigour we have long applied to virology.²⁰

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