NEW APPROACHES TO TREATING CHRONIC VIRAL HEPATITIS B

Rakhmonov R.N.

Master's student, Department of

Infectious Diseases,

Samarkand State Medical University,
Samarkand, Uzbekistan.

Abstract

Chronic hepatitis B virus (HBV) infection remains a major global health problem, affecting over 250 million people worldwide. Despite the effectiveness of nucleos(t)ide analogues and interferon therapy in controlling viral replication, functional cure defined as hepatitis B surface antigen (HBsAg) loss remains rare. This review summarizes recent advances in novel therapies for chronic HBV, their mechanisms of action, and future perspectives for achieving functional cure.

Keywords: chronic hepatitis B, siRNA, capsid inhibitors, CRISPR, therapeutic vaccines, immune modulation, functional cure.

Introduction

Chronic HBV infection is a leading cause of cirrhosis and hepatocellular carcinoma worldwide [1]. Current treatment options are limited to nucleos(t)ide analogues (NAs) and pegylated interferon-alpha (Peg-IFNα). While these therapies suppress viral replication and improve survival, they rarely achieve functional cure. Consequently, new approaches are urgently needed to eliminate cccDNA reservoirs and restore antiviral immunity [2].

Current therapies and their limitations. Nucleos(t)ide analogues such as entecavir and tenofovir effectively inhibit reverse transcription, but long-term therapy is often required, and viral rebound occurs after cessation [3]. Peg-IFNα induces immune-mediated clearance but is limited by tolerability and modest efficacy. Thus, there is an unmet need for therapies that target viral persistence and enhance immune control [4].

Small interfering RNAs and antisense oligonucleotides. RNA interference-based drugs, including siRNAs and antisense oligonucleotides, target viral transcripts, reducing HBsAg production. Clinical trials have demonstrated significant HBsAg decline when siRNAs are combined with NAs [2,8]. These therapies hold promise for breaking immune tolerance by reducing antigen load.

Capsid assembly modulators. Capsid assembly modulators disrupt nucleocapsid formation and block HBV replication at an early stage. Recent phase II trials reported reductions in viral DNA and RNA when combined with NAs [3]. This approach could complement siRNA-based strategies for deeper suppression of HBV replication.

CRISPR-based gene editing. Gene editing technologies such as CRISPR-Cas systems have been investigated for direct targeting of cccDNA, potentially eliminating the viral reservoir. Preclinical studies demonstrated efficient cleavage of cccDNA and reduction in viral replication [4]. However, delivery methods and off-target effects remain key challenges.

Therapeutic vaccines and immune modulation. Therapeutic vaccines aim to restore HBV-specific T cell responses, which are typically exhausted in chronic infection. Several vaccine candidates showed improved immune activity, particularly when combined with siRNAs or immune checkpoint inhibitors [2]. Russian experts, including Surkova and Ivashkin (2021), emphasize the potential of immune-based therapies in combination regimens [5,9]. In recent

years, novel treatment strategies have been developed targeting multiple steps of the HBV life cycle, as well as host immune responses. These include small interfering RNAs (siRNAs), antisense oligonucleotides, capsid assembly modulators, CRISPR-based gene editing, therapeutic vaccines, immune checkpoint inhibitors and combination regimens. Russian researchers also highlight the need to integrate these approaches into clinical practice, considering local epidemiological patterns and treatment availability.

Combination therapies. Most experts agree that no single agent is likely to achieve functional cure. Instead, combination strategies targeting multiple viral and immune pathways appear most promising [1]. Chulanov and colleagues (2023) note that integrating novel antivirals with immunomodulators could optimize outcomes in Russian patients, considering regional genotype distribution [6].

Perspectives. NGS and biomarker-based patient stratification may guide therapy selection in the near future. Bakulin and Ivashkin (2024) suggest that personalized approaches integrating virological and immunological markers are critical for effective therapy implementation in Russia [10].

Conclusion. Novel therapies for chronic HBV are moving beyond viral suppression toward functional cure. siRNAs, capsid inhibitors, CRISPR, and therapeutic vaccines represent exciting advances, especially in combination. Both international and Russian studies [1–7] underline the importance of developing standardized algorithms for integrating these therapies into clinical practice. Achieving functional cure will likely depend on personalized, multi-targeted approaches.

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