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A Comprehensive Review of Direct Acting Antivirals in Chronic Viral Hepatitis Therapy

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Abstract

Chronic viral hepatitis is a global public health concern affecting millions of people worldwide. Traditional treatment options for chronic viral hepatitis, including interferon-based therapies, often had limited efficacy and significant side effects. However, the advent of direct acting antivirals (DAAs) has revolutionized the management of chronic viral hepatitis. In this comprehensive review, we provide an overview of the classes of DAAs available for the treatment of chronic hepatitis B and C, highlighting their mechanisms of action, clinical efficacy, safety profiles, and impact on viral clearance. Additionally, we discuss the challenges and future prospects of DAA therapy, emphasizing the potential for achieving sustained virologic responses and eventually eradicating chronic viral hepatitis.

Keywords: Chronic viral hepatitis; Antiviral; hepatitis C virus

Introduction

Chronic viral hepatitis is caused by the hepatitis B virus (HBV) and hepatitis C virus (HCV) and is a leading cause of liver-related morbidity and mortality globally. Traditional treatment options, such as interferon-based therapies, had limited success in achieving sustained virologic responses and were often associated with significant adverse effects. The emergence of direct acting antivirals (DAAs) has transformed the landscape of chronic viral hepatitis therapy [1].

DDAs on the other hand constitute a more recent development based on increasing knowledge of the molecular biology of the hepatitis viruses. In the case of HCV, the resolution of the 3-dimensional structure of important viral enzymes such as the NS3 serine protease and the RNA dependent RNA polymerase, and the in vitro models of viral replication that have allowed the study of virus entry, replication, morphogenesis, and identified host factors that are required for this process, have been invaluable in the design and testing of drugs under development. Such drugs act directly as viral lifecycle inhibitors [2]. The current choices of treatment will be reviewed in turn for each virus, as well as results from current clinical or preclinical trials with other agents in development, and which most likely will truly revolutionize future treatment approaches.

Classes of direct acting antivirals

DAAs can be classified into different groups based on their targets and mechanisms of action. We discuss the major classes of DAAs, including nucleoside/nucleotide analogs, non-nucleoside polymerase inhibitors, protease inhibitors, and NS5A inhibitors, highlighting how they inhibit viral replication through direct interactions with viral enzymes [3].

Hepatitis B virus

The mature virion or Dane particle measuring 45 nm in diameter is spherical in nature and consists of an outer envelope comprised of the hepatitis B surface proteins in a lipid bilayer derived from the host. The envelope encloses the nucleocapsid of the virus which is composed of the self-assembling core protein. This in turn encloses the viral genome which is a relaxed circular, partially double stranded DNA molecule of 3.2 kb in length. All of the nucleotide sequence of the genome is organized in 4 partially or totally overlapping open reading frames, which are transcribed with the help of two enhancer elements and four promoters within the genome [4]. The Pre-S/S ORF encodes the three envelope glycoproteins which are known as the large (L), middle (M), and small (S) HBsAgs. All three proteins share the S domain, whilst the L and M proteins have N-terminal extensions as indicated. The S domain contains the major hydrophilic region known as the α determinant which confers group specificity, a cluster of B-cell epitopes between amino acid positions 90–160. This constitutes the main target of neutralizing antibodies, both natural and vaccine induced.

DAA therapy for chronic hepatitis B

We review the various DAAs available for the treatment of chronic hepatitis B, focusing on their clinical efficacy and safety profiles. We also discuss their impact on viral load reduction, improvement in liver histology, and potential for achieving sustained virologic responses [5].

Replication

The hepatocyte receptor responsible for virus attachment remains unknown to this date. In contrast, amino acid positions 21–47 of the Pre-S1 have been implicated in virus binding to the hepatocyte membrane. A domain within S may assist in this process by bringing the virion in close contact with the cell membrane, and thus facilitating the specific interaction of the Pre-S1 domain with its receptor. Following internalization the virion is uncoated in the cytosol, the naked core particles are trafficked to the nuclear pore through which the genome penetrates into the nucleoplasm [6], where it is converted into a double-stranded covalently closed circular DNA molecule, following removal of the covalently bonded terminal protein from the negative (−)-DNA strand and repair of the nick, as well as completion and ligation of the shorter positive (+)-strand. Intrahepatic DNA load ranges from 0.1–1 copy per cell, or 10–1000 copies per infected cell, depending on

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the HBeAg status of the patient as explained below. DNA remains in episomal form and in its transcriptionally active state associates with histones and other proteins, and through recruitment of a number of liver specific transcription factors serves as the template for viral transcript synthesis by host RNA polymerase II. Most antiviral agents so far have been unable to prevent the replenishment of the DNA pool from genonic HBV-DNA recycled from immature core particles in the cytoplasm to the nucleus, or to radically eliminate DNA-containing hepatocytes [7].

DAA therapy for chronic hepatitis C

In this section, we provide an in-depth analysis of DAAs used in the treatment of chronic hepatitis C. We explore the different combinations and regimens available, including pan-genotypic therapies, and discuss their high cure rates and shorter treatment durations compared to traditional interferon-based therapies.

Mutations

Natural stable variants of the virus give rise to well-recognized serological subtypes and genotypes. However, HBV has a higher mutation rate than other DNA viruses base substitutions per site per year, through error prone steps in the replication cycle of the virus. These may occur during pgRNA synthesis by the cellular RNA polymerase II, as RNA polymerases show inherently low copying fidelity, but also during reverse transcription due to the lack of proof reading capacity by the viral polymerase [8]. Fluctuations in the composition of the intracellular nucleotide pools are another possible contributing factor. A lot of these mutations are lethal to the virus, but those which offer it a replication advantage facilitate immune escape, or cause resistance to antiviral drugs, as explained later, can be preferentially selected.

Safety and tolerability of DAAs

While DAAs have shown remarkable efficacy, we also critically examine their safety profiles and potential drug interactions. Addressing the challenges related to drug resistance and adverse events is crucial to optimizing treatment outcomes [9].

Challenges and future prospects

Despite the tremendous success of DAAs, several challenges remain, including the cost of treatment, access to therapy in resource-limited settings, and the persistence of chronic hepatitis B covalently closed circular DNA. We discuss ongoing research efforts and potential strategies to overcome these obstacles.

The road to eradication

We conclude the review by highlighting the potential for achieving sustained virologic responses with DAAs and the eventual eradication of chronic viral hepatitis [10]. We emphasize the importance of early diagnosis, increased awareness, and access to affordable treatment to accelerate progress towards global hepatitis elimination goals.

Conclusion

Direct acting antivirals have revolutionized the landscape of chronic viral hepatitis therapy. Their high efficacy, shorter treatment durations, and improved safety profiles have significantly improved patient outcomes. However, challenges such as drug resistance and access to treatment persist. With continued research and collective efforts, the dream of eradicating chronic viral hepatitis could become a reality, ushering in a new era of improved public health and well-being.

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