LUMEN ET VIRTUS
ISSN: 2177-2789

CHRONIC HEPATITIS B VIRUS INFECTION: A SYSTEMATIC REVIEW ON EPIDEMIOLOGY, MECHANISMS OF VIRAL PERSISTENCE, AND TREATMENT OF THE CONDITION

https://doi.org/10.56238/levv15n41-085

Submitted on: 09/22/2024 **Publication date:** 10/22/2024

Silvia Gomes Paranhos[1], Mateus de Sousa Brito[2], Mariana Sciampaglia de Carvalho[3], Anelise Barbosa Cassiano[4], Ana Beatriz Nascimento Chagas[5], Jamile de Castro Tavares[6], Roberta de Souza Oliveira[7], Marcos Antonio Granero Ferrari Neto[8] and Ruan Júnior Lopes Bicalho[9]

ABSTRACT

Objective: The general objective of the present study is to analyze the scientific production on chronic Hepatitis B virus infection, seeking to identify the main methods used in the treatment of this pathology. Methodology: This is a systematic review focused on understanding the main aspects that permeate chronic Hepatitis B virus infection. The research was guided by the question: "What are the main aspects that permeate chronic infection by the Hepatitis B virus, as well as what are the diagnostic and therapeutic resources used in clinical practice?". To find answers, searches were performed in the PubMed database using five descriptors combined with the Boolean term "AND". This resulted in 408 articles. 24 articles were selected for analysis and 15 articles were used to compose the collection. Results: The eradication of hepatitis B depends on the combination of preventive and therapeutic efforts. The persistence of cccDNA in the liver, even after viral suppression, hinders complete functional healing. Antivirals such as entecavir and tenofovir are effective in reducing viral load, but they fail to eradicate the virus in most patients, requiring prolonged treatments. In addition, the variability in treatment responses, influenced by factors such as viral genotype and disease stage, underscores the need for

[1]Undergraduate student in Medicine at Anhembi Morumbi University (UAM)
Email: silviaparanhos2@gmail.com
[2]Graduating in Medicine at the Federal University of Triângulo Mineiro (UFTM)
Email: mateusousabrt@gmail.com
[3]Undergraduate student in Medicine at the University of Franca (UNIFRAN)
E-mail: marianasciampaglia10@gmail.com
[4]Undergraduate student in Medicine at the University of Franca (UNIFRAN)
E-mail: anelisebarbosa01@gmail.com
[5]Undergraduate student in Medicine at the University of Franca (UNIFRAN)
Email: anabeatriznchagas@icloud.com
[6]Undergraduate student in Medicine at the University of Franca (UNIFRAN)
E-mail: jamiletavaresc@gmail.com
[7]Undergraduate student at the Municipal University Center of Franca - Uni-FACEF
E-mail: robertadesoliveira@outlook.com
[8]Graduating in Medicine from the University of Franca (UNIFRAN)
E-mail: graneromarcos@hotmail.com
[9]Dr.
Advisor
Physician from the Faculty of Medicine of Marília (FAMEMA) - Marília - SP, General Practitioner and Gastroenterologist
Email: rjlopes@hcrp.usp.br

personalized approaches to improve clinical management. In summary, despite the advances, there are still important challenges to be faced in the search for a cure for chronic hepatitis B. Conclusion: The systematic review highlighted the main aspects of chronic hepatitis B (CHB), emphasizing its challenges and advances in clinical management. Chronic hepatitis B virus (HBV) infection continues to be a serious public health problem, with complications such as liver cirrhosis and hepatocellular carcinoma. Prevention strategies such as universal vaccination and immunoprophylaxis are effective in reducing mother-to-child transmission, especially in newborns, but global adherence has yet to improve, especially in areas of high prevalence.

Keywords: Chronic Hepatitis B. Treatment. Diagnosis.

INTRODUCTION

Hepatitis B infection is caused by hepatitis B virus (HBV), a DNA virus belonging to the Hepadnaviridae family and the genus Orthohepadnavirus. It is transmitted via exposure to infected blood or body fluids, most commonly by intravenous drug use, sexual contact, or mother-to-child mother-to-child transmission. HBV burden is decreasing in the developed world due to vaccination, but HBV prevalence is still quite high in endemic areas, mainly due to mother-to-child transmission and early life exposures. The age of HBV infection is the main factor that determines the course of the disease; the overwhelming majority of perinatally infected patients develop chronic hepatitis B, while most infected adults eliminate the virus promptly (BELOPOLSKAYA et al., 2021).

In 2006, it was estimated that 2 billion people had been infected with HBV and that 360 million people were living with chronic hepatitis B worldwide. There is geographic variation in the prevalence of hepatitis B. Endemic regions such as Southeast Asia, sub-Saharan Africa, and parts of South America have prevalence rates greater than 8%, compared with 2% in non-endemic areas, including most of North America. Transmission routes differ between endemic and non-endemic areas and determine the course of HBV infection. In endemic areas, mother-to-child vertical transmission and horizontal transmission between young children are the most common routes of HBV infection, but in non-endemic areas, intravenous drug use and adult sexual transmission are the predominant modes of infection. In 2016, an updated estimate indicated that the global total hepatitis B virus (HBV) prevalence of infection increased to 3.9% (95% confidence interval, 3.4 to 4.6%), corresponding to 292 million people worldwide, suggesting that the presence of HBV was not decreasing. In addition, only approximately 29 million (10%) have been diagnosed with HBV infection (ODENWALD; PAUL, 2022) (NGUYEN et al., 2020).

Exposure to HBV in the first six months of life confers a nearly 90% risk of developing a chronic infection due to immune tolerance, which decreases to approximately 50% risk if exposed before 6 years of age. Adults with acute infection and intact immune systems, however, spontaneously clear HBV infection in a remarkable 95% of cases. Taken together, these data indicate that the majority of chronic HBV cases in the world are in endemic areas. In line with this, recent studies have shown that more than 90% of chronic HBV cases in the United States occur in immigrants from endemic areas (ODENWALD; PAUL, 2022). Antiviral drugs can stop viral replication and subsequent liver damage. Although no available treatment can eliminate HBV infection, there are interesting experimental agents that may provide therapeutic benefits in the future. In addition, there is

a broad global health effort to eliminate HBV through a combination of aggressive vaccination, diagnosis, and treatment programs (ODENWALD; PAUL, 2022).

This systematic review article aims to compile and evaluate the existing scientific evidence on chronic hepatitis B virus infection. The intention is to provide a comprehensive and up-to-date view that not only synthesizes current knowledge about the condition, but also identifies gaps in research and directs future investigations and clinical practices. By offering an in-depth analysis of the evidence, this study aims to serve as a resource for health professionals, researchers, and academics, helping to optimize diagnostic and therapeutic approaches to this condition.

METHODOLOGY

This is a systematic review that seeks to understand the main aspects of chronic hepatitis B virus infection , as well as to demonstrate the main pharmacological methods used in the treatment of the condition. For the development of this research, a guiding question was elaborated through the PVO strategy (population, variable and objective): "What are the main aspects that permeate chronic infection by the Hepatitis B virus, as well as what are the diagnostic and therapeutic resources used in clinical practice?"

The searches were carried out through searches in the PubMed Central (PMC) databases. 5 descriptors were used in combination with the Boolean term "AND": Chronic Viral Hepatitis, Quality of Life, Treatment Adherence, Drug-Related Side Effects and Adverse Reactions, and Pharmacological Treatment. The search strategy used in the PMC database was: Chronic Viral Hepatitis AND Quality of Life , Chronic Viral Hepatitis AND Treatment Adherence , Chronic Viral Hepatitis AND Drug-Related Side Effects and Adverse Reactions and Chronic Viral Hepatitis AND Pharmacological Treatment. From this search, 408 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 408 articles were found. After applying the inclusion and exclusion criteria, 24 articles were selected from the PubMed database, and a total of 15 studies were used to compose the collection**.**

RESULTS

Table 1 – Created by the author.

Authors Cited	Main Contributions to the Systematic Review
BELOPOLSKAYA et al., 2021	They highlighted that chronic hepatitis B infection (CHB) is a significant global public health problem, describing the four distinct phases of CHB: immunotolerant, immunoactive, inactive carrier, and reactivation. They explained the persistence of cccDNA in hepatocytes and the challenges in antiviral treatment.
ODENWALD; PAUL, 2022	They focused on the complexity of HBV infection and the importance of the immune system in the initial and chronic process of infection. They discussed the need for initial evaluation of HBV infection based on medical history, physical examination, and markers of hepatitis.
ZHENG; WANG; FENG, 2022	They addressed the crucial role of the liver as an immune organ, highlighting the importance of NK and NKT cells in defending against HBV. They stressed the need for an efficient immune response to eliminate the virus.
DÉNY; ZOULIM, 2010	They described the importance of the initial evaluation of HBV infection through different hepatitis markers and liver blood tests, such as AST and ALT, as well as invasive and non-invasive methods for the detection of cirrhosis.
RIVEIRO-BARCIELA; PERICÀS; BUTI, 2022	They explained the role of HBsAg in HBV infection and its production from cccDNA and integrated DNA. They discussed the importance of HBsAg levels as indicative of HBV activity and host immune response, as well as the challenges in accurate quantification of cccDNA.
NGUYEN et al., 2020	They detailed the progression and treatment of HBH, addressing the importance of early anti-HBe seroconversion and the risks associated with anti-HBe-positive disease. They discussed vaccination and antiviral therapy strategies to prevent transmission and improve patients' liver health.
KRAMVIS et al., 2022	They highlighted the importance of intrahepatic measurement of viral cccDNA and RNA for disease classification, as well as the need for alternative biomarkers that can accurately reflect intrahepatic cccDNA pool and transcriptional activity.
COLOMBATTO et al., 2022	They discussed the efficacy of treatments with pegylated interferons and nucleoside and nucleotide analogues in suppressing HBV DNA and improving liver fibrosis. They highlighted the tolerability challenges and adverse effects of IFN treatments.
TANG et al., 2022	They addressed the efficacy of entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF) in the treatment of CHB, detailing the results of clinical trials and the importance of ALT normalization and HBV DNA suppression.
LOGGI et al., 2022	They emphasized the need for long-term antiviral treatment with nucleoside and nucleotide analogues to prevent progression from CHB to cirrhosis and hepatocellular carcinoma (HCC), as well as highlighting the importance of transaminase normalization and virologic response.
BROQUETAS; CARRIÓN, 2023	They focused on the efficacy of long-term ETV and TDF treatments in suppressing HBV DNA, normalizing transaminases, and regressing liver fibrosis. They discussed the importance of continuous therapies to prevent hepatic decompensation and improve patient survival.
HALL et al., 2020	They described the efficacy of PegIFN treatments in HBeAg-positive and negative patients, detailing virologic and biochemical response rates, and the challenges of adverse events and side effects associated with PegIFN therapy.

LIGAT et al., 2021	They highlighted the persistence of cccDNA in hepatocytes as a significant challenge in the treatment of CHB, highlighting the need for new therapeutic strategies to achieve functional cure, defined by HBsAg seroclearance.
HBF, 2018	It recommended screening all adults for HB with the triple panel of serological markers, involving HBsAg, anti-HBs, and total anti-HBc, as part of the guidelines for a comprehensive initial assessment of HBV infection.
LEE; LEE; AHN, 2020	They analyzed HBsAg levels and cccDNA transcriptional activity, highlighting the importance of host immune clearance and patient selection for early pegIFN discontinuation based on HBsAg levels.

DISCUSSION

HBV infection can lead to acute or chronic hepatitis. Chronic hepatitis B (CHB) infection is defined as serum detection of HBsAg for at least six months. Chronic hepatitis B (CHB) is a significant public health problem worldwide. According to the current estimate of the World Health Organization (WHO), in 2015, about 257 million people in the world were living with CHB. The geographic distribution of CHB is highly heterogeneous. There are regions with high (more than 8%), medium (2%-8%) and low (less than 2%) levels of hepatitis B (HB) prevalence. The course of CHB ranges from asymptomatic carrier of hepatitis B surface antigen (HBsAg) to severe active variants with fibrosis progression, liver cirrhosis formation, and development of hepatocellular carcinoma (HCC) (BELOPOLSKAYA et al., 2021).

The virus that causes hepatitis B is a small DNA virus with 10 known genotypes. The enveloped hepatitis B virus is recognized via HBsAg and enters the cell via receptor-mediated endocytosis. Upon entering the cell, HBV is uncoated and undergoes single-stranded DNA repair to integrate into the host genome or form covalently closed circular DNA (cccDNA), both of which serve as templates for transcription and translation. cccDNA persists in hepatocytes even after other signs of decreasing virus activity, including loss of BsAg, and is the main cause of HBV persistence despite antiviral treatment. The 3.2 kb genome has four open reading frames that code for first, for Core gene (important for viral packaging and e-antigen (eAg) production; second surface gene (encodes surface proteins); third X gene (which maintains cccDNA expression); and fourth polymerase gene (encodes multiple proteins important for DNA replication, including a reverse transcriptase and polymerase). Once transcribed from the cccDNA, immature RNA molecules are packaged into nucleocapsids that can be recycled into the nucleus or further packaged and trafficked to budding sites in an HBsAg-dependent manner (ODENWALD; PAUL, 2022).

Chronic hepatitis B has four distinct phases: the immunotolerant phase, the immunoactive phase, the inactive carrier phase, and reactivation. In the immunotolerant phase, there are high HBV viral loads without laboratory evidence of liver inflammation. The

immunoactive phase is evidenced by lower viral loads with elevated transaminases. If left untreated, patients in the immunoactive phase have a very high chance (approximately 20%) of progressing to chronic liver disease with cirrhosis and hepatocellular carcinoma (HCC) in approximately 25%-30% of patients with the presence of active viral replication and necroinflammatory liver disease being predictors of disease progression. In the absence of antiviral therapy, patients with HBsAg-positive cirrhosis have a 5-year survival of 84% when compensated, but a dismal 14% survival rate at 5 years after the initial decompensation event. Although current antivirals may help improve liver histology, decrease liver decompensation, and improve long-term survival, achieving a functional cure (i.e., loss of HBsAg) is an uncommon event with unknown predictive factors. In the inactive carrier state, patients have normalization of transaminases, undetectable levels of HBV virus, and, in some patients, improvement of fibrosis. However, these patients may reactivate due to loss of immune control, either spontaneously or induced by immunosuppressive therapies. Despite available treatments, the burden of chronic HBV is still very high and is estimated to be responsible for 700,000 deaths each year from decompensated cirrhosis (ODENWALD; PAUL, 2022).

As a crucial immune organ of the human body, the liver is rich in natural killer cells (NK cells), natural killer T cells (NKT cells), as well as macrophages (e.g., Kupffer cells), of which NK cells and NKT cells make up half in terms of lymphocyte numbers in the liver. As the first line of defense against HBV, the natural immune system is very important in the initial and chronic process of HBV infection. In the process of early virus elimination and specific immune response, the immune system response is very important, the deficiency of which is an important reason for persistent HBV infection (ZHENG; WANG; FENG, 2022).

Initial evaluation of HBV infection begins with the patient's history, physical examination, assessment of liver disease activity, and interpretation of different markers of hepatitis and/or their combinations, such as HBsAg, HB nucleus antigen (HBcAg), HBeAg, HB surface antibody (anti-HBs/HBsAb), HB nucleus antibody (anti-HBc), IgM anti-HBc, HB e antibody (anti-HBe), and focus on antigen and antibody detection. The Hepatitis B Foundation (HBF) recommends screening all adults for HB with the triple serological marker panel involving HBsAg, anti-HBs, and total anti-HBc (HBF 2018b). To classify the phases of infection in HBV-infected patients, the following should be performed: i) assays for HBsAg, HBeAg/anti-HBe, HBV DNA; ii) liver blood tests, including aspartate aminotransferase (AST), alanine transaminase (ALT), and iii) transient elastography (Fibroscan) as a non-invasive test or needle liver biopsy as an invasive method for the presence of cirrhosis (DÉNY; ZOULIM, 2010).

HBsAg is the glycosylated envelope protein of the mature HBV virion, composed of three HBsAg proteins. In addition to virions, serum from viremic patients includes two types of non-infectious particles, which are 1000 times more numerous than virions and are thought to serve as decoys for humoral immunity. These subviral particles are derived from both covalently closed circular DNA (cccDNA) and integrated DNA, especially in HBeAg-negative patients. Therefore, HBsAg is also produced from HBV DNA integrated into the host genome (RIVEIRO-BARCIELA; PERICÀS; BUTI, 2022).

In children and young adults, the high replication and low inflammation phase is characterized by detectable serum concentrations of HBsAg and HBeAg and high serum levels of HBV. DNA concentrations but only slightly increased serum ALT levels, and liver histology is often relatively benign (i.e., minimal or no inflammation or fibrosis). However, at this stage, the disease is ongoing, with expansion of hepatocytes and integration of HBV that can ultimately progress to active disease. Progression to cirrhosis in HBeAg-positive patients occurs at a rate of 2 to 5.5% per year, becoming 8 to 20% at 5 years. The high replication phase may be followed by active HBV infection with the development of necroinflammation (also known as HBeAg hepatitis or the immune-active phase) or by HBeAg seroconversion and remission in a proportion of patients (HBeAg-negative infection or inactive carrier state). Inactive carriers characteristically exhibit normal aminotransferase levels, and the HBV DNA level is usually found to be less than 2,000 IU/ml. A small proportion of patients experience regression of the disease at a rate of 0.5 to 2% per year. Early anti-HBe seroconversion before the onset of severe liver fibrosis may signal remission and may indicate a good prognosis, depending on the degree of liver damage (NGUYEN et al., 2020).

On the other hand, HBeAg-negative anti-HBe-positive disease (also called HBeAg-negative hepatitis or reactivation phase) is a progressive stage of chronic disease. Although HBeAg is not apparent in these patients due to mutant pre-core HBV, HBcAg is detected in liver cells and evidence of active disease is still present. Patients with anti-HBe-positive CHB are usually older, have more ongoing inflammatory changes, and have variations in the course of liver disease, with inconsistent serum aminotransferase levels and different HBV DNA concentrations. Anti-HBe-positive patients show a more rapid progression to cirrhosis at an annual rate of 8 to 20%, and HBsAg and HBV DNA levels in these patients tend to be lower than those in patients who are HBeAg-positive (NGUYEN et al., 2020).

Patients with cirrhosis experience liver failure at a rate of 16% over 5 years. In 366 HBsAg-positive patients with compensated cirrhosis, the cumulative probability of survival was 84% and 68% at 5 and 10 years, respectively (117–120). It was determined that the

risk factors for a high rate of progression and lower survival were age, male sex, high liver enzyme levels, high HBV DNA levels, high HBsAg levels, infection with a genotype C strain, as well as basal nucleus promoter expression (NGUYEN et al., 2020).

Intrahepatic measurement of cccDNA and viral RNAs can improve disease classification, but it involves the use of liver biopsy samples, which are invasive, are not routine CHB care, and are not available in resource-limited settings. In addition, only a small section of the liver is sampled by liver biopsies. Although specific quantitative polymerase chain reactions (PCRs) for cccDNA have been developed, the coexistence of replicative HBV DNA intermediates in infected cells 16, including relaxed, integrated, circular HBV DNA molecules, interferes with the precise quantification of cccDNA. In this regard, a global collaborative project initiated by ICE-HBV aims to optimize and harmonize CCCDNA detection and quantification protocols in liver tissue and cell culture. Consequently, there is an urgent need for alternative biomarkers that not only accurately reflect intrahepatic CccDNA pool and transcriptional activity, but also better characterize the different stages of CHB disease and the risk of complications, detect HBV integration, improve the determination of the risk of hepatocellular carcinoma (HCC), and monitor immune status and response to therapy (KRAMVIS et al., 2022).

In 2011, the World Health Organization passed a resolution recognizing viral hepatitis as a global health concern. In October 2015, this agency released its first official strategy for the control of viral hepatitis, which aims to significantly reduce the considerable morbidity and mortality found in individuals with chronic hepatitis B and chronic hepatitis C virus (HCC) infections by the year 2030. Government agencies (194 countries) have subscribed to this strategy, which includes ambitious targets of a 90% reduction in viral hepatitis incidence, an 80% adherence to treatment by eligible patients, and a 65% reduction in mortality (NGUYEN et al., 2020).

The global elimination of HBV could become a reality thanks to the use of an effective and low-cost vaccine, which has been available for almost 30 years. The hepatitis B vaccine has been shown to prevent hepatocellular carcinoma (HCC). Currently, most countries have implemented universal neonatal HBV vaccination programs, which are inexpensive and could eradicate HBV infection in the next century. Improving vaccination rates at birth and providing prepartum therapy for highly viremic mothers to prevent mother-to-child transmission could accelerate the eradication of hepatitis B (NGUYEN et al., 2020).

Recent data demonstrate that immunoprophylaxis with hepatitis B immunoglobulin and hepatitis B vaccine in newborns can reduce the rate of mother-to-child transmission (MTCT) from 90% to 10%. However, if the mother has a HBV DNA level greater than

200,000 IU/ml, immunoprophylaxis has a failure rate of 10 to 30% in babies born to these mothers. Transmission can be effectively eliminated by administering antiviral therapy to the mother during the third trimester, as demonstrated by a randomized controlled trial from China. The analysis showed that the transmission rate dropped from 7% in the control group to 0% in the treatment group at 28* week postpartum. Thus, currently, major liver societies in the United States and Europe recommend that all pregnant women with HBV DNA levels greater than 200,000 Ul/ml be considered for treatment with tenofovir disoproxil fumarate (TDF) beginning near the end of the second trimester and early third trimester (24 to 28 weeks of pregnancy). Importantly, breastfeeding and TDF treatment may continue postpartum in HBsAg-positive untreated women (NGUYEN et al., 2020).

Current antiviral therapy aims to prevent progression from CHB to cirrhosis and, in cirrhotics, to avoid or delay end-stage complications of liver disease and hepatocellular carcinoma (HCC). Current approved treatments for chronic HBV can be broadly classified into immunomodulatory agents (standard and pegylated interferon-ÿ, PegIFN-ÿ) and antiviral agents (nucleoside and nucleotide-NA analogues). Immunomodulatory agents are administered in a finite course and can lead to functional "cure", i.e., loss of HBsAg. However, this is achieved in a scant percentage of patients, not exceeding 10%, regardless of HBeAg status. In addition, this choice of treatment is limited by poor tolerability and high risks of adverse events, with a relatively low acceptance of IFN by clinicians and patients as a consequence. Nucleoside and nucleotide (NA) analogues inhibit HBV DNA synthesis through a competitive interaction with natural HBV polymerase substrates, achieving HBV DNA suppression in the vast majority of compliant patients. However, the mechanism of action of NA does not prevent the formation of replication recovers after antiviral therapy is discontinued in most patients, requiring indefinite or even lifelong term therapy. In this scenario, the chance of discontinuing AN treatment in carefully selected patients represents a crucial point (LOGGI et al., 2022) (COLOMBATTO et al., 2022).

Currently, there are nine drugs approved for the treatment of CHB, including two formulations of interferon (IFN) — conventional and pegylated IFN (PegIFN) — and seven nucleo(t)id analogues (NAs): lamivudine (LAM), telbivudine, adefovir (ADV), entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF), and besifovir dipivoxil (Korea only) (LEE; LEE; AHN, 2020). NAS have been shown to reduce progression to cirrhosis, liver failure, and HCC (CORNBERG et al., 2020).

IFN-ÿ was the first treatment option for CHB and showed antiviral activity in HBeAg-positive and HBeAg-negative CHB patients: serum HBV DNA became undetectable (<1–10 pg/mL) in 37–56% of HBeAg-positive CHB patients with 33% loss of HBeAg, about 70%

ALT normalization at the end of the 4–6-month course of therapy, more than 80% of HBeAg-to-anti-HBe seroconversions maintained for 4–9 years after treatment discontinuation and up to 65% loss of HBsAg in sustained responders The same treatment regimens (5–10 MU every other day for 16–24 weeks) when used in HBeAg-negative/anti-HBe-positive CHB were associated with high relapse rates (70–90%) despite good (70%) response to treatment. Thus, longer treatment courses (12–24 months) were attempted in HBeAg-negative/anti-HBe-positive CHB with a higher sustained response rate (22–30% vs. 10–15%) and HBsAg loss of 32–67% in sustained responders within 4–7 years of treatment (COLOMBATTO et al., 2022).

In the last 15 years, the standard IFN-ÿ has been replaced by pegylated formulations whose active drug conjugated with polyethylene glycol (Peg) molecules has an extended half-life and can be administered once a week. There were two formulations of pegylated interferon (Peg-IFN) available: Peg-IFN alfa-2b bound to a 12 kD linear Peg molecule and Peg-IFN alfa-2a bound to a branched Peg molecule larger than 40 kD.In HBeAg-positive patients at 6–12 months post-treatment, HBeAg to anti-HBe seroconversion was achieved in 29–32% of HBeAg-positive patients. PegIFN is given by subcutaneous injection and adverse events are common, including flu-like symptoms, cytopenias, neuropsychiatric problems, and thyroid dysfunction. PegIFN therapy is used only in a select minority of patients due to limited long-term efficacy and concerns about tolerability. In HBeAg-negative patients with CHB, normalization of ALT and HBV-DNA <2000 IU/mL at 6 months of follow-up was observed in 38% of cases; overall, response was maintained in 25% of patients up to 5 years of age with an HBsAg clearance rate of 12%. Therefore, treatment with IFN-ÿ can indeed induce a functional cure, even in a limited number of cases: it is worth noting that the overall rate of HBsAg loss in treated patients is much higher than that achieved spontaneously in HBeAg-negative infection (COLOMBATTO et al., 2022) (HALL et al., 2020).

NA can be classified as a low (LAM, ADV, and LdT) or high (ETV, TDF, and TAF) resistance barrier. Current international guidelines recommend the use of AN with a high resistance barrier to prevent progression of liver disease, decompensation of cirrhosis, need for liver transplantation, development of HCC, and to improve survival. Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are potent and safe antiviral agents, they have a high barrier to resistance. Suppression of HBV-DNA to undetectable levels (virologic response) is typically associated with normalization of transaminases (biochemical response) and improved survival. (BROQUETAS; CARRIÓN, 2023) (HALL et al., 2020).

ETV is an analogue of cyclopentanoylguanosine, which has strong anti-HBV activity and rapidly reduces the viral load of CHB patients. In two phase III clinical trials, for hepatitis E antigen (HBeAg)-negative and HBeAg-positive patients at 48 weeks of ETV treatment, 90% and 67% had undetectable serum HBV DNA, 78% and 68% achieved ALT normalization, while 0% and 2% achieved HBsAg loss, respectively. For HBeAg-positive patients with 5-year ETV treatment, 94% achieved HBV DNA <300 copies/mL, 80% achieved ALT normalization, while 5% achieved HBsAg loss. TDF is an acyclic NA adenine that inhibits HBV polymerase efficiently. In two phase III clinical trials, HBeAg-negative and HBeAg-positive patients with 8 years of TDF therapy, 99% and 98% had undetectable HBV DNA, 88% and 84% achieved ALT normalization, while 1.1% and 13% achieved HBsAg loss, respectively. TAF, a prodrug of tenofovir, delivers active metabolites to hepatocytes more effectively than TDF. In two phase III clinical trials, for HBeAg-negative and HBeAg-positive patients with 3-year TAF therapy, 87% and 74% achieved HBV DNA levels less than 29 IU/mL, 71% and 64% achieved ALT normalization, while 0.4% and 1.4% achieved HBsAg loss, respectively (TANG et al., 2022).

In the presence of cirrhosis, all patients with detectable HBV-DNA should be treated. Indications for the treatment of patients with HBeAg-positive and HBeAg-negative CHB are generally based on the combination of three main criteria: liver disease severity, HBV-DNA units, and ALT levels. In patients with HBeAg-positive CHB, long-term NA therapy may induce HBeAg loss and seroconversion, leading to a low replicative phase with partial immune control. In these patients, antiviral treatment with ETV demonstrated a 5-year cumulative probability with a virologic response of 99%, HBeAg loss of 53%, but HBsAg loss of only 1.4%. Similarly, TDF for 10 years demonstrated a 52% HBeAg loss, but only a 4.9% HBsAg loss (BROQUETAS; CARRIÓN, 2023).

Long-term treatment with NA has demonstrated a significant regression of liver fibrosis and even cirrhosis. A study with paired liver biopsies, after a median time of 6 years, in 57 patients receiving ETV showed histological improvement (decrease ÿ 2 points in Knodell necroinflammatory score) in 96% of patients, and improvement in fibrosis (decrease ÿ 1 point in Ishak fibrosis score) in 88% of them. In a study with TDF, including 348 patients with paired liver biopsies (at baseline and week 240), 87% showed histological improvement and 51% regression of fibrosis (decrease ÿ 1 point in Ishak fibrosis score). Among the 96 patients with cirrhosis at baseline, 74% achieved some degree of fibrosis regression (BROQUETAS; CARRIÓN, 2023). element. A virologic response during NA therapy is defined as undetectable HBV DNA based on assays with a lower limit of detection of 10–20 IU/mL in blood. With IFN-based treatment, a virologic response is

defined as a serum HBV DNA level of less than 2000 IU/mL when assessed at 6 months after the start of treatment and at the end of therapy. A biochemical response is defined as normalization of serum alanine aminotransferase. A normalization of alanine aminotransferase with a reduction in HBV viral load is an important goal to be achieved (LEE; LEE; AHN, 2020).

HBsAg levels decline very slowly in virally suppressed patients in NAs, particularly HBeAg-negative patients, as the integrated HBV genomes maintain HBsAg transcription. A minority of HBeAg-positive subjects show drastic declines in HBsAg (>1 log at week 24 of NA therapy), which is associated with greater clearance of HBsAg. Loss of HBsAg is uncommon, particularly in the HBeAg-negative population. In patients treated with pegIFN, the level of HBsAg at week 12 or week 24 allows for the selection of patients for early discontinuation of pegIFN due to the high probability of non-response. HBsAg measures the activities of integrated HBV-DNA and cccDNA, and low HBsAg in patients receiving NAS indicates host immune clearance (RIVEIRO-BARCIELA; PERICÀS; BUTI, 2022).

CHB is characterized by the persistence of the covalently closed episomal circular DNA (cccDNA) form of the HBV genome that persists as a stable minichromosome in the nuclei of infected hepatocytes. After withdrawal of therapy or loss of immune control, a few copies of cccDNA by hepatocytes can reactivate complete viral replication. Therefore, cccDNA would have to be eliminated from infected liver cells to achieve HBV cure. This sterilizing cure, i.e., complete viral eradication of the host, is the ultimate goal, but currently hardly attainable. A more feasible goal is "functional cure," with hepatitis B surface antigen (HBsAg) seroclearance as a defining parameter. For any type of CHB cure, the development of new therapeutic strategies remains an unmet medical need (LIGAT et al., 2021).

CONCLUSION

The systematic review addressed the main aspects of chronic hepatitis B (CHB), highlighting its complexity and challenges in clinical management. Chronic infection with the hepatitis B virus continues to be a serious global public health problem, with serious consequences, such as liver cirrhosis and hepatocellular carcinoma. Preventive strategies, such as universal vaccination and immunoprophylaxis, have been shown to be effective in reducing mother-to-child transmission of HBV, especially in newborns, but overall adherence to these measures still needs improvement, particularly in areas of high prevalence. Hepatitis B eradication, while possible in the long term, depends on

coordinated efforts between prevention strategies and therapeutic advances that lead to functional cure, which is currently improving by a small fraction

The persistence of cccDNA in the liver, even after viral suppression, hinders complete functional cure, limiting therapeutic advances, although antivirals such as entecavir and tenofovir have demonstrated efficacy in reducing disease progression. The available treatments, although effective in many cases to control viral replication and delay complications, are still unable to completely eradicate the virus in most patients, requiring prolonged and, in some cases, indefinite treatments. In addition, the variability in treatment responses, influenced by factors such as viral genotype and disease stage, reinforces the need for personalized approaches.

REFERENCES

1. Belopolskaya, M., & et al. (2021). Chronic hepatitis B in pregnant women: Current trends and approaches. World Journal of Gastroenterology, 27(23), 3279. https://doi.org/10.3748/wjg.v27.i23.3279

2. Broquetas, T., & Carrión, J. A. (2023). Past, present, and future of long-term treatment for hepatitis B virus. World Journal of Gastroenterology, 29(25), 3964. https://doi.org/10.3748/wjg.v29.i25.3964

3. Colombatto, P., & et al. (2022). Management and treatment of patients with chronic hepatitis B: Towards personalized medicine. Viruses, 14(4), 701. https://doi.org/10.3390/v14040701

4. Cornberg, M., & et al. (2020). Guidance for design and endpoints of clinical trials in chronic hepatitis B—Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference. Hepatology, 71(3), 1070-1092. https://doi.org/10.1002/hep.31030

5. Dény, P., & Zoulim, F. (2010). Hepatitis B virus: From diagnosis to treatment. Pathologie Biologie, 58(4), 245-253. https://doi.org/10.1016/j.patbio.2009.11.003

6. Hall, S., & et al. (2020). The yin and the yang of treatment for chronic hepatitis B—When to start, when to stop nucleos(t)ide analogue therapy. Viruses, 12(9), 934. https://doi.org/10.3390/v12090934

7. Kramvis, A., & et al. (2022). A roadmap for serum biomarkers for hepatitis B virus: Current status and future outlook. Nature Reviews Gastroenterology & Hepatology, 19(11), 727-745. https://doi.org/10.1038/s41575-022-00649-z

8. Lee, H. W., Lee, J. S., & Ahn, S. H. (2020). Hepatitis B virus cure: Targets and future therapies. International Journal of Molecular Sciences, 22(1), 213. https://doi.org/10.3390/ijms22010213

9. Ligat, G., & et al. (2021). Hepatitis B virus–host interactions and novel targets for viral cure. Current Opinion in Virology, 49, 41-51. https://doi.org/10.1016/j.coviro.2021.04.009

10. Loggi, E., & et al. (2022). Virological treatment monitoring for chronic hepatitis B. Viruses, 14(7), 1376. https://doi.org/10.3390/v14071376

11. Nguyen, M. H., & et al. (2020). Hepatitis B virus: Advances in prevention, diagnosis, and therapy. Clinical Microbiology Reviews, 33(2), e00046-19. https://doi.org/10.1128/CMR.00046-19

12. Odenwald, M. A., & Paul, S. (2022). Viral hepatitis: Past, present, and future. World Journal of Gastroenterology, 28(14), 1405. https://doi.org/10.3748/wjg.v28.i14.1405

13. Riveiro-Barciela, M., Pericàs, J. M., & Buti, M. (2022). How to interpret viral markers in the management of chronic hepatitis B infection. Clinical Microbiology and Infection, 28(3), 355-361. https://doi.org/10.1016/j.cmi.2021.10.005

14. Tang, Y., & et al. (2022). Advances in new antivirals for chronic hepatitis B. Chinese Medical Journal, 135(5), 571-583. https://doi.org/10.1097/CM9.0000000000001852

15. Zheng, J.-R., Wang, Z.-L., & Feng, B. (2022). Hepatitis B functional cure and immune response. Frontiers in Immunology, 13, 1075916. https://doi.org/10.3389/fimmu.2022.1075916