Review Article
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Drug treatment of chronic hepatitis b in Brazil: a review

Abstract

Hepatitis B is a liver infection caused by the *Hepatitis B virus*, which can be chronic, exposing the population to a high risk of death from cirrhosis and liver cancer. The treatment of HBV in Brazil is currently carried out according to the protocol of therapeutic guidelines, which recommends the use of drugs Tenofovir, Entecavir, Adefovir, Lamivudine, Interferon-alpha and Peg-interferon. The aim of this study is to demonstrate aspects of drug therapy for chronic hepatitis B in Brazil. This study was carried out through a bibliographic review, in the databases PubMed, "Scientific Electronic Library Online" (SciELO) and Google Academics, in the period from 2011 to 2021. A total of thirty-four scientific articles were analyzed. In general, the drugs recommended for the treatment of chronic hepatitis B in Brazil are nucleoside inhibitors of reverse transcriptase and immunomodulators. These drugs have several adverse reactions, such as headache, nausea, vomiting, abdominal pain, diarrhea, dizziness. The choice of treatment may be influenced by the HBV got more effective, with less adverse reactions and that increase the patient's adherence to the treatment, enabling a better quality of life.

Keywords: hepatitis B chronic, *Hepatitis B virus*, therapy, antiviral

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Abbreviations: HBV, hepatitis B viruses; SVR, sustained virological response; SVR, sustained virological response; LMV, lamivudine; ADV, adefovir; ETV, entecavir; TDF, tenofovir

Introduction

According to the WHO, world health organization (2021),[1] hepatitis B is a liver infection caused by the HBV, *Hepatitis B virus*, imminently fatal and a major global health problem. HVB causes chronic infection, being the most communicable, exposing the population to the severity of the disease and high risk of death from cirrhosis and liver cancer.

Hepatitis B can occur asymptomatic or symptomatically, when symptomatic it presents as oligosymptomatic.[2] It is known, then, to be imminently fatal, as it is a very serious disease, as viral hepatitis is considered to represent the largest reason for liver transplants in the world.[3] In 2019, according to the assessment of the WHO, 296million individuals developed chronic hepatitis B virus infection, in that same year 820,000 died, mainly from cirrhosis and hepatocellular carcinoma.[1] In 2016, only 10.5% (27million) lived with the level of infection and 17% (4.5million) received treatment.[4]

The current treatment of chronic HBV is limited; however, it can be improved with the evolution of new drug production technologies. There are two classes of therapy available: (I) immunomodulators and (II) NRTI, nucleoside reverse transcriptase inhibitors, both of which in turn can reduce the possibility of developing viral resistance and thus achieving a SVR, sustained virological response.[5] Therefore, it is essential to develop new alternatives for antiretroviral treatments against chronic hepatitis B, in addition to carrying out resistance tests, in order to obtain a reduction in the evolution of the disease and a definitive cure for hepatitis B.

Thus, the objective of this study was to carry out an updated bibliographic review on the drugs recommended in Brazil for the treatment of hepatitis B, demonstrating the mechanisms of action of antiviral, as well as specifying the main adverse reactions presented by antiviral applied in the treatment of hepatitis B.

Material and methods

This study aimed to carry out an applied research based on data available in the literature, through an exploratory research carrying out an integrative review on aspects of drug treatment for chronic hepatitis B. Articles published from 2000 to 2021 in Portuguese and English were considered as inclusion criteria. Articles that were not published in full and that were duplicated in the databases were excluded from the study. The bibliographic research was carried out by consulting databases with significant health knowledge: PubMed, "Scientific Electronic Library Online" (SciELO) and Google Academics, with the keywords "Hepatitis B chronic" (Hepatite b crônico), "Therapy" (Terapia) and "Antiviral" (Antiviral). The selection of scientific articles took place first by analyzing the title and reading the abstracts, those that had information relevant to the topic were analyzed in full. As for ordinances and bulletins of the Ministry of Health, they were extracted from the same updated data on the epidemiology of the disease and information regarding the diagnosis and treatment recommended in Brazil for Hepatitis B.

Results and discussion

The search in the databases using the descriptors resulted in a total of 5,976 references (132 in SciELO; 3,364 in PubMed; 2,480 Google Scholar). Of these 3,954 were in duplicates indexed in more than one database. Being 2,022, they were screened by reading their title and abstract, which resulted in only 592 articles being read in full to confirm eligibility.

Of these, 288 were excluded for not meeting the need for the research and lack of criteria in the drug treatment of hepatitis B. In addition, journals that did not meet the objective of the study and published prior to 2010, about 270 articles were disregarded. , so the present study involved in its conception about 34 scientific articles. Six drugs are currently available for the treatment of chronic hepatitis B: four nucleoside/nucleotide analogues lamivudine (LMV), adefovir (ADV), entecavir (ETV), tenofovir (TDF); and two interferon-based treatments (conventional interferon alpha and pegylated interferon

alpha). Nucleoside/nucleotide analogues suppress viral replication by inhibiting HBV viral polymerase, whereas interferon therapy improves host immune response.[6]

Two important characteristics of antiviral drugs must be considered: potency and genetic barrier to resistance. The ideal drug is potent and has a high genetic barrier to resistance.[7] All these agents are capable of suppressing HBV replication, but SVR is not frequent, occurring in less than 20% of treated patients, SVR is equivalent to a cure for HBV infection, decreasing the chance of disease progression.[2]

Nucleoside/nucleoside analogs

Nucleotide/nucleoside analogues selectively neutralize DNA, Deoxyribonucleic acid, polymerase, nullifying the viral load, providing seroconversion of HBeAg, hepatitis B e-antigen, achieving standardization of ALT, alanine aminotransferases, with an increase in liver fibrosis as a consequence of viral clearance.[8] The duration of therapy depends mainly on seroconversion from HBeAg to anti-HBe and from HBsAg, Hepatitis B surface antigen, to anti-HBs, which can last from six months to five years. They are generally well tolerated by patients and severe adverse events are rarely encountered.[9,10]

The advantages of using nucleotide/nucleoside analogues include oral availability and high patient acceptability, early control of hepatitis (fall of ALT) and considerable improvement in liver histology; the latter including interruption or partial reversal of fibrosis if viral suppression can be maintained. Disadvantages are relatively low rates of sustained post-treatment response (hence prolonged therapy is required in most cases) and a high rate of drug resistance. This resistance is often followed by a resumption of hepatitis activity.[11]

Lamivudina

LMV was approved by the US, United States, FDA, Food and Drugs Administration in 1998 as the first nucleoside analogue for the treatment of chronic hepatitis B. LMV is incorporated into the growing strand of DNA during reverse transcription of the first strand of DNA and synthesis of the second, resulting in inhibition of HBV-DNA synthesis.[10]

LMV is effective in suppressing viral replication in both HBeAg positive and HBeAg negative patients and is associated with histological improvement, HBeAg seroconversion and ALT normalization.[7] The biggest problem with long-term therapy with this drug is drug resistance. There is a low genetic barrier to LMV resistance (the lowest among current drugs), amplifying resistance with a mutation. As a result, the use of LMV monotherapy is not recommended as the first choice for the treatment of chronic hepatitis B, both in HBeAg positive and negative patients.[12]

Its use is applied in short-term therapy, as protection against reactivation during chemotherapy, last trimester of pregnancy in pregnant women with high viral load (usually greater than 100million copies/mL) or fulminant hepatitis by HBV, despite effectiveness in the latter situation has not yet been proven.[7]

LMV is a drug considered safe from a pharmacological point of view, with few reports of adverse reactions, and therefore, it is one of the most used NRTIs in antiretroviral therapy regimens.[2]

Diarrhea may occasionally arise while using the medication. Dose reduction has been shown to be necessary in patients with renal failure.[13]

Adefovir

It is a nucleotide analogue (adenosine) that acts by inhibiting HBV reverse transcriptase. It is potentially nephrotoxic. It is an acyclic that acts as a DNA chain terminator and induces the production of endogenous INF.[14] HBeAg positive patients, after one year of treatment with this drug, showed histological improvement, reduced serum levels of HBV-DNA and high rates of HBeAg seroconversion. When the treatment is prolonged for over a year, the benefits of therapy with this drug are even greater.[15]

ADV has a low potency and a genetic barrier to median resistance. Its use in monotherapy should be continued only in patients who reach HBV-DNA negative after 48weeks of treatment.[12] When the patient is resistant to this drug, can be used in conjunction with LMV.[10]

ADV manifests persistence that can result in viral load rebound, which in turn can cause exacerbation of hepatitis B and, in a scenario of decreased liver function, lead to liver decompensation, with possible fatal consequences.[5] To mitigate the risk of resistance in patients who do not respond to lamivudine, adefovir dipivoxil should be used in combination with lamivudine rather than as monotherapy. In order to reduce the risk of resistance in patients receiving adefovir dipivoxil as monotherapy, treatment modification should be considered if serum HBV DNA levels remain above 1,000 copies/ml.[16]

According to ANVISA's, Agência Nacional de Vigilância Sanitária, CPTG, Clinical Protocol and Therapeutic Guidelines, for Hepatitis B and Co-infections, after oral administration, adefovir dipivoxil is rapidly biotransforming to adefovir. At concentrations substantially higher (>4,000-fold) than those observed in vivo, adefovir did not prevent any of the following CYP450, Cytochrome P450, isoforms: CYP1A2, CYP2D6, CYP2C9, CYP2C19, CYP3A4. Based on the responses of this in vitro knowledge and the known extinction pathway of adefovir, the potential for CYP450-mediated interactions involving these drugs with other medicinal products is low.[2]

Very common reactions (occur in 10% of patients who use this drug) can cause the absence or loss of muscle strength. On the other hand, common reactions (occur between 1% and 10% of patients who use this drug) can cause abdominal pain, nausea, flatulence, intestinal discomfort/gas), diarrhea, poor digestion, headache.[16]

Entecavir

ETV is a nucleoside analogue (guanosine) that inhibits three steps of HBV replication: the initiation of HBV DNA polymerase[17]. Reverse transcription of HBV-DNA negative strand from pregenomic messenger RNA; and HBV-DNA positive strand synthesis. It is the most potent antiviral among the current nucleoside/nucleotide analogues approved for use in patients with chronic hepatitis B, in addition to having a high genetic barrier, requiring three mutations for the patient to develop drug resistance.[7,12]

After four years of ETV therapy, in patients who had not previously used nucleoside/nucleotide analogues, less than 1% of patients did not show resistance to therapy.[9,10] ETV was active not only in HBeAg positive patients, but also in HBeAg negative patients and in LMV resistant patients.[10,18]

The most common adverse events of any severity (≥3%) were: Headache, fatigue, dizziness and nausea. 1% of patients treated with Entecavir, discontinued due to adverse events or abnormal laboratory test results.[2]

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Clinical adverse effects in nucleoside-naive patients were evaluated. Where, 679 use ETV 0.5mg once a day for an average time of 54weeks. Adverse reactions of moderate or severe potency and leading to treatment with ETV are insomnia; nervous system disorders, 30 such as headache, uncommon, dizziness, drowsiness; gastrointestinal disorders such as nausea, diarrhea, dyspepsia, vomiting and; and general disorders such as fatigue.[16]

Tenofovir

TDF was initially approved for the treatment of HIV infection. It is phosphorylated in its active form, and binds directly with HBV DNA polymerase thus suppressing viral replication.[10]

TDF is structurally similar to ADV, but it is less nephrotoxic, which proves that it is applied in higher doses, increasing its effectiveness. Many studies show a good efficacy of TDF in patients with resistance to LMV, yet it has less potency in patients with resistance to ADV.[8] Thus, like ETV, TDF has a high potency and good genetic barrier to resistance.[7]

Tenofovir disoproxil fumarate in the body is transformed into tenofovir, which prevents viral polymerases from attaching directly to them. TDF has minimal intervention in the synthesis of human DNA, which leads to greater safety in its use. When patients receive Tenofovir Desoproxil Fumarate concomitantly with lopinavir/ritonavir, atazanavir boosted with ritonavir or darunavir should be monitored for adverse reactions associated with Tenofovir Desoproxil Fumarate. In patients who develop adverse reactions to Tenofovir Desoproxil Fumarate associated with it, it should be discontinued.[2]

Treatment-emergent adverse reactions reported in >5% of patients treated with Tenofovir Desoproxil Fumarate included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain and rash.[2]

Interferons

Interferon's are a group of immunoregulatory proteins synthesized by T lymphocytes, macrophages, fibroblasts and other types of cells, after being stimulated with viruses, antigens, mitogens, double-stranded DNA or lectins. Synthesized for therapeutic purposes, they were the first medications approved for the treatment of HBV infection. Interferon increases the ability of macrophages to destroy tumor cells, viruses and bacteria. They block viral replication, potentiate NK, natural killer, cell lytic activity, increase MHC, major histocompatibility complex, class I expression in virus-infected cells, and induce Th1, type 1 T helper, cell development. They are capable of preventing viral replication, are anti-proliferative and fever-inducing. Have an immunomodulatory effect.[8]

Furthermore, they increase seroconversion from HBeAg to anti-HBe, however, their benefit is achieved in only one third of treated patients, and no advantages in prolonging the time of therapy were observed.[6,18]

We currently have the formulations interferon α, pegylated interferon α and human interferon α 2b. Pegylated interferon α has shown greater efficacy and easier administration when compared to the conventional one. The interferon α 2b formulation has also shown good results in HBeAg positive patients, with 50% seroconversion to anti-HBe. In addition to these formulations, interferon λ has been recently described, which belongs to the class of type III interferon, however little is known about them. Studies in murine liver cells have shown that interferon λ is able to inhibit HBV replication with the same efficiency as interferon α. In humans, however, the results are still not well defined.[19]

Interferons are rarely tolerated due to their severe side effects, which involve flu-like illnesses, anorexia, autoimmune disease outbreaks, thyroid dysfunction, myelosuppression, hepatitis outbreaks, hepatic decompensation and adverse neuropsychiatric events such as depression, irritability and eventual moodiness to suicide[10]

Interferon-α

Interfero-α (IFN-α) was the first drug licensed for the treatment of hepatitis B. IFN has two forms of presentation, conventional or pegylated (peginterferon). Pegylation allows the drug to work longer in the body. The pregylation process covalently binds an Interferon molecule to a polyethylene glycol molecule.[20]

Interferons are glycoproteins that have numerous biological behaviors, including antiviral, immunomodulatory, and complex antiproliferative consequences. Its endogenous production and release occurs in response to viruses and other inducers, with the exception of bacterial exotoxins, polyanions, some low molecular weight compounds and microorganisms with intracellular growth.[21,22]

It points out that the mechanism by which recombinant human interferon alpha 2a and other types of interferon carry out anti-tumor and antiviral activity is not entirely common. However, it is believed that a direct antiproliferative action on the inhibition of viral replication and modulation of the host's immune response plays an important role in the antiviral activity.[16]

According to the data demonstrated by ANVISA, the advantage of administering Interferon alpha is the treatment for a defined period (48-52weeks), but side effects and contraindications may arise in patients with decompensated liver cirrhosis. Interferon alpha 2a is required to be used under medical advice. People with abnormal kidney, liver and bone marrow function should be carefully monitored.[2] Ordinance No. 2561/09 shows that care must be taken when using recombinant human interferon alpha 2a in people with myelosuppression (suppression of the bone marrow blood cell production function), as recombinant human interferon alpha 2a can cause reduction of the white blood cells.[2] This parameter should be carefully monitored prior to initiation of interferon alpha 2a therapy and at designated times during therapy. Complete blood tests must be performed periodically.[16]

The most frequent adverse reactions have flu-like symptoms such as fatigue, fever, chills, muscle pain, headache, joint pain, sweating, among others. They may also present gastrointestinal changes, such as anorexia, nausea, vomiting, change in taste, weight loss, diarrhea, abdominal pain, constipation, flatulence.[2]

Liver function should also be noted, some patients had increased levels of alkaline phosphatase, lactic acid, dehydrogenase and bilirubin. Normally the dose of recombinant human interferon alpha 2a should not be adjusted when such reactions occur.[2,23]

Reactions can also affect the central nervous system, causing dizziness; visual disturbances, memory loss, depression, drowsiness, anxiety, nervousness and insomnia were observed in rare cases and peripheral nervous system, showing paresthesia, torpor, weakness.[2,23]

Skin changes in the form of Herpes, rash, itching and dry skin that are occasionally reported. Hair loss has been observed in one fifth of patients receiving recombinant human interferon alpha 2a. In the urinary system, according to the author, renal failure was rarely

observed. Electrolyte disturbances occasionally occur in association with anorexia and dehydration.[16]

The hematopoietic system may be affected, generating transient leukocytopenia which has occurred in one third of half of patients receiving recombinant human interferon alpha 2a. Thrombocytopenia and decreased hemoglobin are seen in some patients with bone marrow depression. Severe normality in the hematopoietic system can be reversed 7 to 10 days after discontinuation of recombinant human interferon alpha 2a therapy. [2,23]

PEG Interferon alpha-2a

PEG-interferon alfa-2a is a biological response transformer. The coupling of PEG reagent (bis-monomethoxypolyethylene glycol) with interferon alfa-2a forms a pegylated interferon alfa-2a. According to ANVISA data, interferon bind to specific receptors on the cell surface, initiating a complex pathway of intracellular signaling and rapid activation of gene transcription. Interferon-activated genes articulate several biological effects, achieving inhibition of viral replication in infected cells, inhibition of cell proliferation and immunomodulation.[23]

Alpha interferon can affect the oxidative metabolic process, reducing the activity of CYP450 liver microsomal enzymes. However, subcutaneous administration of 180mg Pegasys® once weekly for 4weeks to healthy male subjects had no effect on enzymes.[23]

According to ANVISA's CPTG for Hepatitis B and co-infections, the most common reactions with no defined incidence are abdominal pain, lack of appetite, diarrhea, nausea, decreased neutrophils in the blood, anemia, decreased lymphocytes in the blood, joint pain, muscle pain, hair loss, itching, depression, dizziness, fatigue, headache, insomnia, irritability.[2,23]

Conclusion

The mechanisms of action of drugs recommended for the treatment of chronic hepatitis B in Brazil can be either by the inhibitory action of viral replication or by modulation of the immune system, causing several adverse reactions.

The evolution of drugs used in the treatment of chronic hepatitis B is necessary, in order to achieve a more effective treatment, taking into account that the patient must have greater adherence to treatment, always seeking to avoid interruptions. Therefore, further research is needed so that the mechanism of action and adverse reactions of current drugs are evidenced, so that an advance in the production of new drugs can occur, always aiming for an evolution in the treatment of chronic hepatitis B.

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Conflicts of interest

We declare there is no conflict of interest.

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References

1. World Health Organization. Hepatitis B. Geneva: World Health Organization; 2021.
2. Brasil. Protocolo Clínico e Diretrizes Terapêuticas para Hepatite B e Coinfecções. 2017.
3. Sherman M, Shafran S, Burak K, et al. Management of chronic hepatitis B: Consensus guidelines. *Can J Gastroenterol.* 2007;21(Suppl C):5C–24C.
4. WHO urges countries to invest to eliminate viral hepatitis. Geneva: World Health Organization; 2021.
5. Almeida AM, Ribeiro AQ, Menezes de Pádua CA, et al. Efficacy of adefovir dipivoxil, entecavir and telbivudine for the treatment of chronic hepatitis B: systematic review. *Rev Soc Bras Med Trop*. 2010;43(4).
6. Aspinall EJ, Hawkins G, Fraser A, et al. Hepatitis B prevention, diagnosis, treatment and care: A review. *Occup Med (Lond)*. 2011;61(8):531-540.
7. Bhattacharya D, Thio CL. Review of hepatitis B therapeutics. *Clin Infect Dis*. 2010;51(10):1201-1208.
8. Koumbi L. Current and future antiviral drug therapies of hepatitis B chronic infection. *World J Hepatol.* 2015;7(8):1030–1040.
9. Wiens A, Correr CJ, Pontarolo R. CHRONIC HEPATITIS B: A REVIEW ON CLINICAL AND THERAPEUTIC ASPECTS. *Visão Acadêmica*. 2010;11(2).
10. Lam YF, Yuen MF, Seto WK, et al. Current antiviral therapy of chronic hepatitis B: Efficacy and safety. *Curr Hepat Rep*. 2011;10(4):235–243.
11. Farrell GC, Teoh NC. Management of chronic hepatitis B virus infection: A new era of disease control. *Intern Med J*. 2006;36(2):100–113.
12. https://repositorio.ufba.br/ri/bitstream/ri/5715/1/5899-16364-1-PB%5B1%5D.pdf
13. Lok ASF, McMahon BJ. Chronic hepatitis B. *Hepatology*; 2007;45(2):507–539.
14. Gerlich WH. Medical Virology of Hepatitis B: How it began and where we are now. *Virol J*. 2013;10:239.
15. Tang CM, Yau, TO, Yu J. Management of chronic hepatitis B infection: Current treatment guidelines, challenges, and new developments. *World J Gastroenterol*. 2014;20(20):6262–6278.
16. Marmentini M. Pharmaceutical care for hepatitis B virus carriers. 2011;50.
17. Wong DKH, Kopaniszen M, Omagari K, et al. Effect of hepatitis B virus reverse transcriptase variations on entecavir treatment response. *J Infect Dis*. 2014;210(5):701–707.
18. Ferreira MS, Borges AS. Advances no treatment of hepatite hair virus B. *Rev Soc Bras Med Trop*. 2007;40(4).
19. Robek MD, Boyd BS, Chisari FV. Lambda Interferon Inhibits Hepatitis B and C Virus Replication. *J Virol*. 2005;79(6):3851-3854.
20. Araujo NM, Vianna COA, Moraes MTB, et al. Expression of hepatitis B virus surface antigen (HBsAg) from genotypes A, D and F and influence of amino acid variations related or not to genotypes on HBsAg detection. *Brazilian J Infect Dis.* 2009;13(4):266-271.
21. Koyama S, Ishii KJ, Coban C, et al. Innate immune response to viral infection. *Cytokine*. 2008;43(3):336–341.
22. Lorenzi JCC, Coelho-Castelo AAM. Resposta imune contra infec es virais. *Scire Salut*. 2011.
23. Clinical Protocol and Therapeutic Guidelines for the Treatment of Chronic Viral Hepatitis B and Coinfections. Brazil: Ministry of Health Health Surveillance Department STD, AIDS and Viral Hepatitis Department. 2011.