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Review article

Treatment of chronic hepatitis B: options, monitoring, special cases and adverse effects

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Abstract:

Introduction:

Hepatitis B remains a significant clinical issue. Despite the availability of effective vaccines, the world is still not free from this problem. Chronic hepatitis B virus (HBV) infection affects approximately 296 million people worldwide and is the leading cause of cirrhosis and liver cancer globally. HBV-related cirrhosis resulted in an estimated 331,000 deaths in 2019, and it is estimated that the number of deaths from HBV-related liver cancer in 2019 was 192,000, an increase from 156,000 in 2010. The rate of vaccination is particularly unsatisfactory in low-income countries, but even in high-income countries, the issue of hepatitis B has not been completely eradicated.

Aim of the study: The aim of this paper is primarily to systematize knowledge regarding the natural course of HBV infection and therapeutic options for chronic hepatitis B, both in adults and children. It also aims to highlight the principles of monitoring pharmacotherapy. The paper also describes therapeutic possibilities in special cases, such as pregnancy, liver transplantation, and the initiation of immunosuppressive therapy. Attention is also given to the potential adverse effects of pharmacotherapy.

Material and methods:

Literature available in the PubMed database was reviewed using the following keywords:

“hepatitis”; “hepatitis B”; “chronic hepatitis B treatment”; “interferons”; “nucleo(t)side analogs”; “hepatitis B monitoring therapy”; “children hepatitis B”; “hepatitis B pregnancy”;” hepatitis B immunosuppression”; “interferons side effects”; “nucleo(t)side analogs side effects”

Conclusions:

As hepatitis B infection continues to pose a significant global health challenge and remains the leading cause of liver cirrhosis and hepatocellular carcinoma, it is essential to review the available treatment options for this condition. Even in Europe, where vaccination coverage has reached high levels, cases of hepatitis B are still detected, often incidentally. This review aims to provide an in-depth analysis of therapeutic approaches for chronic hepatitis B, considering factors such as patient age, clinical status, and liver fibrosis stage. Additionally, it emphasizes the importance of monitoring treatment efficacy and safety, while also addressing the potential adverse effects associated with antiviral therapy.

Keywords: “hepatitis”; “hepatitis B”; “hepatitis B treatment”; “hepatitis B treatment side effects”; “hepatitis B monitoring therapy”; “hepatitis B special cases”

1.Introduction

Chronic hepatitis B is a condition lasting more than 6 months, characterized by necro-inflammatory alterations resulting from persistent HBV infection.[1] HBV infection can be transmitted through 3 ways:

- parenteral (bloodborne) route: The most common route of transmission is through contact with infected blood. This can occur through blood transfusions, sharing needles and syringes among intravenous drug users, and unsafe medical procedures (e.g., in countries with low healthcare standards);

- vertical transmission (from mother to child): HBV can be transmitted to the newborn during childbirth, particularly if the mother is a carrier or has an active infection. In such cases, the risk of infection to the newborn can be as high as 90%;
- sexual transmission: HBV can be spread through sexual contact, particularly among individuals with multiple sexual partners and those engaging in high-risk sexual practices (e.g., without protection).[2]

The incubation period for HBV ranges from 4 to 24 weeks (average 12 weeks). Acute infection manifests in about 50% of adults and 10% of children. Symptoms include fatigue, persistent muscle and joint pain, jaundice, and sometimes pruritus. Some patients, especially older individuals, may present acute infection as multiple episodes of acute hepatitis occurring over approximately 3 months. In 90% of adults, the infection does not progress to chronic infection, and therefore, cirrhosis and subsequently hepatocellular carcinoma (HCC) do not develop. These patients do not require routine antiviral treatment. However, 90% of children infected with HBV and 10% of adult patients develop chronic hepatitis B. They require antiviral therapy. The cure rate, however, is very low. Seroconversion in the HBs system (disappearance of HBsAg and appearance of anti-HBs antibodies) occurs in only 1% of treated patients.[3] The factors that promote the progression of acute hepatitis B to chronic form include:

- perinatal infection
- a high dose of viral particles causing the infection
- anicteric course of the acute phase
- mild course of the acute phase
- low ALT activity during the acute phase
- male gender
- advanced age
- immunosuppression
- use of glucocorticoids during the prodromal and acute phase of the disease

2.Symptoms of infection

Most patients with chronic hepatitis B do not experience symptoms. Occasionally, these patients report chronic fatigue and a depressed mood. On physical examination, mild

hepatomegaly is common, and in more severe cases, jaundice (either persistent or intermittent) may be observed. After many years of the disease, splenomegaly may develop, indicating the presence of portal hypertension. In some cases, the initial signs of chronic liver disease are linked to advanced cirrhosis, or extrahepatic manifestations such as nodular arteritis or membranous glomerulonephritis may occur. These symptoms result from the presence of immune complexes. Periodic flare-ups of chronic inflammation may sometimes resemble acute hepatitis.[4]

3.Natural course of the disease

Viral hepatitis B typically progresses through consecutive phases. These include phases with active liver inflammation as well as phases with low disease activity (*inflammatory/non-inflammatory*).

1. High replication phase with positive HBeAg – the patient's serum shows the presence of both HBsAg and HBeAg, with elevated HBV-DNA levels. Alanine aminotransferase (ALT) levels are typically within the normal range or mildly elevated.
2. Immunoreactive phase with positive HBeAg – HBV-DNA levels are variable, but generally lower than in the previous phase. Periodic elevations in ALT levels are observed, typically more pronounced than in phase one. Hepatic inflammatory changes are mild to moderate, with varying degrees of fibrosis. This phase may persist for months or years, and in approximately 2-15% of patients, seroconversion to anti-HBe occurs (sometimes followed by reseroconversion and the reappearance of HBeAg). The frequency of flares correlates with the progression of hepatic fibrosis.
3. Inactive HBV carrier state – anti-HBe antibodies are present, HBV-DNA levels are low, and ALT activity is minimal. Histological changes in liver biopsy depend on the frequency and severity of inflammatory changes from the previous phase. During this phase, there are minimal inflammatory changes and fibrosis of varying degrees. The risk of progression to cirrhosis and HCC exists, with the disappearance of HBsAg and the development of anti-HBs antibodies occurring in approximately 1-3% of patients annually.
4. HBeAg-negative chronic hepatitis – in nearly 30% of patients following seroconversion in the HBe system, inflammation in the liver persists. HBV-DNA

levels and aminotransferase levels fluctuate. This phase is characterized by periods of exacerbation and remission, with necroinflammatory changes also fluctuating.

5. Latent infection phase (HBsAg-negative) – This phase is typically characterized by very low or undetectable HBV-DNA levels in the serum, with detectable levels in the liver. Serological tests during this phase reveal the presence of anti-HBc and anti-HBs antibodies, or solely anti-HBc antibodies. Seroconversion in the HBs system is associated with a reduced risk of developing cirrhosis and liver failure; however, the risk of hepatocellular carcinoma (HCC) remains elevated compared to the general population. Due to the presence of the episomal form of the virus (cccDNA) in hepatocytes, there is a risk of reactivation in immunocompromised individuals.[4,5,6]

4.Principles of initiating treatment for chronic hepatitis B

Complete eradication of HBV from the infected individual remains impossible. Due to the insensitivity of the episomal form of cccDNA to available treatments, the goal is to achieve complete suppression of HBV replication (which can be confirmed using real-time PCR) and seroconversion in the HBs system (disappearance of HBsAg and the appearance of anti-HBs antibodies).[7] The primary objectives of antiviral therapy are to prevent the development of cirrhosis and hepatocellular carcinoma (HCC), prolong and improve the patient's quality of life, and inhibit the spread of the infection. Furthermore, treatment is also aimed at normalizing biochemical markers of liver inflammation and achieving seroconversion in the HBe system (disappearance of HBeAg and the development of anti-HBe antibodies).[8]

Antiviral treatment is indicated for both HBeAg(+) and HBeAg(-) patients who have detectable HBsAg in their serum for at least 6 months. Additionally, these patients must meet at least two of the following three criteria:

1. Presence of HBV-DNA levels greater than 2000 IU/ml
2. ALT activity exceeding the upper limit of normal
3. Evidence of hepatic inflammation or fibrosis, assessed through liver biopsy with histopathological examination (now rarely performed) or via elastography measuring liver stiffness (a result above 7 kilopascals indicates advanced fibrosis and qualifies the patient for antiviral therapy without the need for a biopsy).

In patients under 30 years of age without clinical signs of liver damage and a family history of hepatocellular carcinoma, antiviral treatment and liver biopsy are not required. In this group, ALT levels should be monitored every 3 months, and liver stiffness should be assessed using elastography. If elevated enzyme activity or signs of liver fibrosis are detected, antiviral therapy should be initiated. In patients with a family history of cirrhosis or HCC, inflammation and fibrosis should be assessed. If features of chronic inflammation are present, treatment should be initiated promptly. Patients with advanced cirrhosis should receive treatment regardless of HBV-DNA levels. Before starting therapy, it is mandatory to screen for HCV and HIV infections in all patients. If ALT levels increase or remain elevated during treatment, anti-HDV IgG antibodies should be tested. [4]

5.Drugs used in the treatment of chronic hepatitis B

In Europe, several substances have been approved for the treatment of chronic hepatitis B. These can be divided into two major drug groups: interferons and analogs. The interferons include natural interferons, α2a and α2b, as well as pegylated α2a. The nucleoside analogs include lamivudine, telbivudine, and entecavir, while the nucleotide analogs include adefovir and tenofovir. The most effective interferon is pegylated α2a, which is administered once a week. Currently, the use of natural and non-pegylated interferons is not recommended. The preferred analogs are entecavir and tenofovir, as they exhibit the strongest antiviral activity and are effective against many HBV genotypes. Among other analogs, the antiviral activity is lower. The use of lamivudine or adefovir may be associated with the risk of selecting resistant strains, which could limit therapeutic options for HBV and contribute to the spread of drug-resistant strains.[9,10]

Interferons

In Poland, genotype A is the predominant variant responsible for chronic hepatitis B.[11] Consequently, the preferred first-line treatment is pegylated interferon α2a. The treatment duration with this agent is strictly defined. For patients without contraindications to 48-week interferon therapy (such as decompensated cirrhosis), it should be the treatment of choice. If the pharmacotherapy proves ineffective, after the planned completion of treatment, therapy with entecavir or tenofovir should be initiated. In some cases, interferon therapy may need to be discontinued before the full 48-week course. Such situations arise when there is no reduction in qHBsAg or HBV-DNA levels in patients undergoing interferon therapy. The

criteria for a proper response to treatment vary depending on whether the patients are HBe-Ag(+) or HBe-Ag(-), as well as the virus genotype responsible for the infection. The effects of interferon therapy are not immediately apparent. Seroconversion in the HBs system may take several years after discontinuation of therapy. Therefore, the minimal initial goal of interferon therapy should be to reduce HBV-DNA levels to less than 2000 IU/ml. After treatment completion, ALT activity, HBV-DNA, and HBs-Ag levels should be assessed. If HBV-DNA levels or ALT activity increase, antiviral therapy should be reinitiated. In such cases, nucleotide analogs (entecavir or tenofovir) should be used. Interferon therapy should not be restarted.[12]

Nucleo(t)side analogs

Treatment with analogs should lead to the suppression of HBV replication below the detection threshold in serum (HBV-DNA levels below 15 IU/ml). This generally correlates with improvements in hepatic biochemical and histopathological parameters. During pharmacotherapy, HBV-DNA levels and ALT activity should be monitored (up to 4 times a year). Antiviral therapy with analogs is considered effective if, in HBe-Ag(+) patients, anti-HBe antibodies are produced, HBs-Ag is eliminated, and seroconversion to anti-HBs occurs. There is no definitive temporal criterion for discontinuing therapy with nucleotide/nucleoside analogs. It is generally accepted that the disappearance of HBe-Ag, the appearance of anti-HBe, and the maintenance of this status for 12 consecutive months with normal ALT activity and viremia below 2000 IU/ml may constitute an indication to end treatment. After completing therapy, due to the risk of reseroconversion, regular monitoring of HBe-Ag/anti-HBe is necessary. HBV-DNA levels should also be measured. HBs-Ag should be measured every 12 months from the appearance of anti-HBe antibodies. For patients who were initially HBe-Ag(-), the efficacy of analog therapy is assessed by evaluating the elimination of HBs-Ag from the body and seroconversion to anti-HBs. This occurs very rarely, and therefore, these patients require ongoing therapy with analogs. HBV-DNA testing is also performed every 12 months (to consider changing the therapy if viremia is detectable) and HBsAg/anti-HBs (to determine if treatment should be discontinued). If HBs antigen is eliminated, treatment should be continued until anti-HBs antibodies appear. If therapeutic goals are not achieved despite appropriately selected antiviral therapy, HBV drug resistance testing should be conducted.[13,14]

Monitoring therapy

The following types of responses to treatment are distinguished:

1. Complete response - undetectable HBV-DNA and seroconversion to anti-HBs
2. Virological response - undetectable HBV-DNA, but HBs-Ag is present
3. Partial virological response - partial reduction in HBV-DNA levels compared to baseline, but it remains detectable for 6 months of treatment
4. Virological breakthrough - an increase in HBV-DNA levels by at least 1 log10 IU/ml in a patient with previously undetectable viremia; usually associated with the selection of drug-resistant strains and referred to as secondary drug resistance
5. Primary drug resistance - no reduction in viremia of at least 1 log10 IU/ml compared to baseline within 3 months of treatment (most often caused by infection with a drug-resistant strain of the virus)

Sometimes, primary drug resistance, partial virological response, or virological breakthrough can be misdiagnosed. Conditions with similar characteristics may be caused by patients not adhering to therapeutic recommendations.[12]

Management of therapeutic failures

In cases of therapeutic failure (lack of response to interferon treatment after 24 weeks post-therapy), a potent analog, such as entecavir or tenofovir, should be initiated. If treatment with these analogs does not produce the desired results, the first consideration should be patient non-compliance with the prescribed regimen. Following this, antiviral resistance testing should be conducted. If the patient is found to be infected with a strain exhibiting significant resistance to treatment, the current drug should be switched to another within the same class – entecavir should be replaced with tenofovir, tenofovir with entecavir, and if lamivudine was used as first-line therapy, it should be replaced with either tenofovir or entecavir. In cases of partial response to monotherapy, the addition of a second drug from the same class can be considered. This is particularly relevant for patients with high baseline HBV-DNA levels who have shown a substantial reduction in viral load during treatment with a single agent. A combination of entecavir and tenofovir is recommended. In patients initially treated with analogs who exhibit drug resistance or a partial virological response, the possibility of treatment with interferon should be considered. Patients who adhere to therapeutic guidelines and have low viremia (<100 IU/ml) should continue their current therapy.[15-18]

6.Special cases in the management of chronic hepatitis B

Treatment of chronic hepatitis B in children

Adolescents over the age of 14 are treated the same as adults. The decision to initiate treatment in younger children is primarily based on ALT activity. If ALT levels are normal, the presence of HBeAg and HBV-DNA should be tested. Patients with detectable HBeAg or serum HBV-DNA levels above 20,000 IU/ml are considered to be in an immunotolerant state. Those without detectable HBeAg or with HBV-DNA levels below 2,000 IU/ml are classified as inactive carriers. Neither of these groups requires chronic treatment, as it would involve the risk of developing drug resistance. Regular monitoring of liver function is recommended. If ALT activity exceeds the upper limit of normal by at least 1.5 times, or if it is above 60 IU/ml in two measurements, and HBV-DNA is confirmed, the activity of liver inflammation and the degree of liver fibrosis should be assessed. Minimal inflammatory activity or fibrosis does not indicate the need for treatment. In cases of moderate or advanced inflammatory activity or fibrosis, appropriate treatment should be initiated.[19] In European Union countries, PEG-IFN-α2a is registered for the treatment of children and is characterized by high efficacy.[20] In Poland, only recombinant interferon α2b is reimbursed.[12] In clinical trials, good results were also achieved in the adolescent population with the use of analogs such as entecavir and tenofovir.[21-23] Situations in children that require special attention and often constitute indications for the initiation of antiviral therapy include worsening liver function, cirrhosis, HBV-induced glomerulonephritis, prophylaxis for HBV recurrence after liver transplantation, recipients of transplants from anti-HBc(+) donors, immunosuppression, chemotherapy, co-infection with HIV or other viral hepatitis, and a family history of hepatocellular carcinoma (HCC).[12]

The principles of therapy for other special cases of HBV infection are presented in the table below.

Situation	**Treatment**
cirrhosis and hepatocellular carcinoma caused by HBV infection	patients with cirrhosis and detectable HBV-DNA should be treated with analogs – entecavir at a dose of 0.5 mg or tenofovir; in this group of patients, PEG-IFN-α2a should be avoided.[24]
chronic hepatitis B in women planning pregnancy	in infected women who do not have advanced liver fibrosis, antiviral therapy should be deferred until after childbirth; women with advanced liver fibrosis should be treated with PEG-IFN-α2a prior to pregnancy; the physician should inform the woman about the need for contraception during the use of this medication; if the woman has contraindications to interferon treatment, tenofovir or telbivudine should be used[25]
chronic hepatitis B in pregnant women	interferons are contraindicated during pregnancy, while lamivudine and entecavir are classified as Category C, and telbivudine and tenofovir are classified as Category B; if woman being treated for chronic HBV becomes pregnant, interferon (if used) should be discontinued first; the preferred treatment during pregnancy is tenofovir (the decision to continue, change, or discontinue treatment is made based on the assessment

	of liver function and the degree of fibrosis, the patient should remain under the care of a hepatologist throughout the entire pregnancy)[26,27]
antiviral therapy in liver transplant recipients	if HBV-DNA is detectable, antiviral therapy with analogs (entecavir/tenofovir) should be initiated before transplantation and the start of immunosuppression; in patients who are only positive for total anti-HBc, prevention of HBV reactivation should include the administration of hepatitis B surface immunoglobulin (HBIG) in the peri-transplant period and the use of antivirals (AN) throughout the period of immunosuppression; if the donor was anti-HBc positive, antiviral therapy should be continued for life; if the donor was anti-HBc negative, antiviral therapy should be continued for one year post-transplant[12,28,29]
prevention of HBV reactivation in individuals planned for or undergoing immunosuppressive therapy (chemotherapy, biological treatment) *the highest risk is associated with the use of rituximab, fatumumab, ustekinumab, natalizumab, alemtuzumab, ibritumomab, doxorubicin, epirubicin, prednisone (above 10 mg daily for more than 4 weeks), infliximab, adalimumab, certolizumab, and golimumab*	HBV reactivation is defined as a sudden, at least 100-fold increase in HBV DNA levels in individuals with previously detectable HBV DNA or the reappearance of detectable HBV DNA in individuals who did not have detectable viremia prior to the initiation of immunosuppressive, biological, or cancer chemotherapy; HBsAg-positive individuals must have their HBV-DNA levels tested, and if the result is positive, they should receive analogs throughout the treatment period and for at least 6 months

	after its completion; in cases of high-risk medications for reactivation, this period should be extended to 12 months; HBsAg-positive patients with undetectable HBV-DNA and HBsAg-negative patients with detectable total anti-HBc, who are planned to undergo high or medium risk reactivation therapy, should also start antiviral therapy before initiating immunosuppressive treatment; the preferred treatment is entecavir or tenofovir; in individuals who are anti-HBs negative and are planned to undergo immunosuppressive therapy, hepatitis B vaccination should be considered[30,31]

7.Adverse effects of treatment

The treatment of hepatitis B, both with interferons and analogs, is associated with the risk of adverse drug reactions.

Interferons

In the case of interferon use, side effects may include anorexia, insomnia, concentration disorders, shortness of breath, diarrhea, nausea, abdominal pain, hair loss, dermatitis, irritability, neutropenia, herpes, upper respiratory tract infections, and fungal infections.[32,33] One of the most serious complications of interferon use is the development of severe depression, even among patients with no prior psychiatric history. Depression is associated with suicidal attempts, some of which may be successful. Therefore, patients taking interferon must be made aware that if they experience mood changes or suicidal thoughts, they should urgently seek psychiatric help.[34-36]

Nucleo(t)side analogs

The most common side effects of analogs include upper respiratory tract infections, headaches, fatigue, elevated ALT and CK levels (most often not requiring discontinuation of treatment),

dizziness, and nausea. In the case of tenofovir, a decrease in bone mineral density has also been reported (more frequently in patients treated for HIV infection).[37]

8.Conclusions

Hepatitis B remains an unresolved, significant clinical problem worldwide. Current treatments are not ideal and lack high efficacy. Patients infected with HBV who develop the chronic form of the disease experience significantly reduced quality of life and have a very high risk of developing cirrhosis and hepatocellular carcinoma. Given the presence of episomal cccDNA, which is permanently integrated into the hepatocytes of infected individuals, it seems extremely difficult to discover a drug that would effectively cure the chronic infection and prevent complications, as was achieved in the case of HCV. Therefore, particular attention should be paid to effective vaccination as the greatest achievement in the fight against HBV, especially ensuring access to vaccines in low-income countries. Unfortunately, even with effective vaccines, chronic HBV infections will still occur, which is why it is important to understand the principles of managing patients presenting with such a condition.

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