Review

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The Problem of Access to Hepatitis B Treatment in the Balkan Country of North Macedonia

Balkan Ülkesi Kuzey Makedonya'da Hepatit B Tedavisine Erişim Sorunu

Marija Dimzova, Mile Bosilkovski, Boban Toshevski

Ss. Cyril and Methodius University Faculty of Medicine, Department of Infectious Diseases, Skopje, North Macedonia

ABSTRACT

Chronic hepatitis B (CHB) virus infection represents a global public health threat that causes considerable liver-related morbidity and mortality. In chronically infected patients, an elevated serum hepatitis B virus (HBV)-DNA concentration is the main risk factor for disease progression, although other clinical and viral characteristics can influence disease outcomes. At present, curing HBV infection is challenging in most patients and they need long-term antiviral treatment. The first-line treatments are nucleos(t)ide analogs (NAs) with a high barrier to resistance: tenofovir and entecavir, while in highly selected patients, an alternative treatment option is regulated interferon. Long-term therapy with NAs is safe and well tolerated, achieves potent viral suppression, and reduces the incidence of liver-related complications. For the majority of patients with CHB in North Macedonia, the current anti-HBV treatment is lamivudine with a low genetic barrier, which leads to compensatory mutations and resistance. With current vaccine strategy, applying therapies with effective high genetic barrier to resistance drugs, and improved linkage to care we should improve the treatment for patients with CHB and strive toward the World Health Organization goal of eliminating HBV as a global health threat by 2030.

Keywords: Hepatitis B virus, chronic hepatitis B, nucleos(t)ide analogs, pegylated interferon, lamivudine, entecavir, tenofovir

ÖZ

Kronik hepatit B (KHB) virüsü enfeksiyonu, önemli ölçüde karaciğerle ilişkili morbidite ve mortaliteye neden olan küresel halk sağlığı tehdidini temsil eder. Kronik olarak enfekte hastalarda, yüksek serum hepatit B virüsü (HBV)-DNA konsantrasyonu, hastalığın ilerlemesi için ana risk faktörüdür, ancak diğer klinik ve viral özellikler hastalık sonuçlarını etkileyebilir. Şu anda, HBV enfeksiyonunu iyileştirmek çoğu hastada zordur ve bu hastaların uzun süreli antiviral tedaviye ihtiyaçları vardır. Birinci basamak tedaviler, yüksek direnç bariyeri olan nükleos(t)id analoglarıdır (NAs): Tenofovir ve entecavir, çok seçilmiş hastalarda alternatif tedavi seçeneği pegile interferondur. NAs uzun süreli tedavi güvenlidir ve iyi tolere edilir, güçlü viral baskılama sağlar ve karaciğerle ilişkili komplikasyonların insidansını azaltır. KHB bulunan hastaların çoğunluğu için mevcut anti-HBV tedavisi, telafi edici mutasyonlara ve dirence yol açan düşük genetik bariyerli lamivudindir. Mevcut aşı stratejisi, dirençli ilaçlara karşı etkili, yüksek genetik bariyeri olan tedaviler ve bakım bağlantısının iyileştirilmesi ile KHB hastalarının tedavisini iyileştirmeli ve Dünya Sağlık Örgütü'nün HBV'yi 2030 yılına kadar küresel bir sağlık tehdidi olarak ortadan kaldırma hedefine doğru çaba göstermeliyiz.

Anahtar Kelimeler: Hepatit B virüsü, kronik hepatit B, nükleoz(t)id analogları, pegile interferon, lamivudin, entekavir, tenofovir

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Introduction

Chronic infection with hepatitis B virus (HBV) represents a global health problem with over 296 million people being chronic HBV surface antigen (HBsAg) carriers, with 1,2 million new infections every year. According to the World Health Organization (WHO) in 2019, hepatitis B resulted in estimated 820,000 deaths, mostly from cirrhosis and hepatocellular carcinoma. At the same time, it has been estimated that 3.8% of the world population is living with chronic hepatitis HBV infection (1,2). Regardless of the vaccines, chronic hepatitis B (CHB) remains the predominant cause

Address for Correspondence: Marija Dimzova MD, Ss. Cyril and Methodius University Faculty of Medicine, Department of Infectious Diseases, Skopje, North Macedonia
E-mail: marijadimzova@hotmail.com **ORCID ID:** orcid.org/0000-0002-1799-8079 **Received:** 20.04.2023 **Accepted:** 16.06.2023

of chronic liver disease and liverrelated morbidity worldwide due to different vaccination policies and migration. CHB is considered to be the major risk factor for cirrhosis, endstage liver disease, and hepatocellular carcinoma (HCC), depending on host and viral factors (3). The natural history of CHB is complex and represents an interplay of virological, environmental, and host factors, and the infected patients can go through different phases during their disease. These phases differ between each other in terms of HBV-DNA serum levels, extent of liver diseases and disease progression toward liver fibrosis, which can be gradual, accelerated and sporadic. Schematically, the natural history of chronic HBV infection can be divided into five phases, taking into account the presence of hepatitis B e antigen (HBeAg), HBV-DNA levels, alanine aminotransferase (ALT) values and eventually the presence or absence of liver inflammation (4,5) (Figure 1).

The new nomenclature is based on the description of two main characteristics of chronicity: infection vs. hepatitis. The first phase is considered to represent a state of immune tolerance when HBeAg is positive, serum HBV-DNA levels are very high, HBV infectivity is high with normal ALT levels, and there is little if any liver damage. Vertical HBV transmission in neonates is very high in this phase, but horizontal HBV transmission can also occur. The second immune-reactive phase is associated with liver necroinflammation and fibrosis and is referred to as HBeAg-positive CHB, but the terms immune reactive, immune active, or HBeAg clearance phase are also used. HBeAg is positive, HBV-DNA levels are usually high but can vary, ALT levels are increased, and liver histology shows necroinflammation with variable stages of fibrosis. The phase of HBeAg-positive CHB may end not only in HBeAg seroconversion but also in HBsAg clearance and seroconversion to anti-HBs. However, in some patients, HBV replication continues despite HBeAg loss and the development of hepatitis B e antibodies (anti-HBe), and there is little if any residual viral replication, the so-called "inactive HBsAg carrier state" or the third phase. The majority of patients remain for a lifetime in an inactive carrier state, spontaneous clearance of HBsAg can occur in 1-3% of cases per year. The fourth

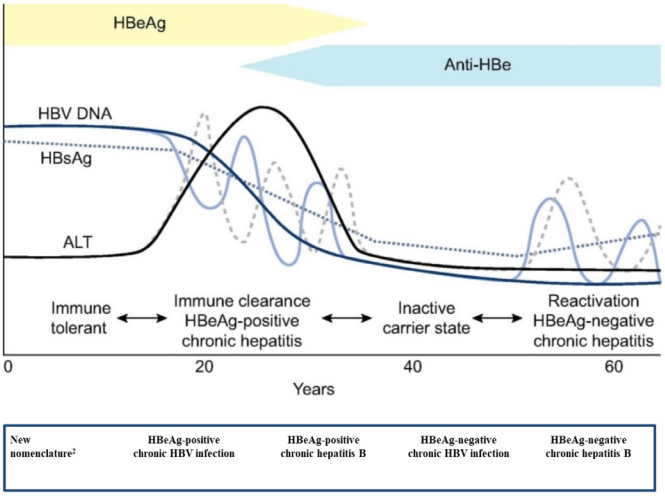

Figure 1. Phases of chronic HBV infection (4)

HBeAg: Hepatitis B e antigen, HBV: Hepatitis B virus, HBsAG: Hepatitis B surface antigen, ALT: Alanine aminotransferase, anti-HBe: Hepatitis B e antibody

phase is so called HBeAg-negative CHB, characterized by the lack of serum HBeAg usually with detectable anti-HBe and persistent or fluctuating moderate to high levels of serum HBV-DNA, mostly lower than in HBeAg-positive patients; fluctuating or persistently elevated ALT values with hepatic necroinflammation and fibrosis. There are very low rates of spontaneous disease remission in this phase. In the fifth HBsAg- negative phase, the resolution of CHB is characterized by negative HBsAg, with or without detectible anti-HBs antibodies in the patients serum. Immunosuppression might lead to HBV reactivation in these patients, hence the term "occult HBV infection" (4).

The Epidemiology of Chronic HBV Infection in the Republic of North Macedonia

According to the prevalence of chronic HBsAg carriers, different geographic areas in the world are designated as areas with low (2%), intermediate (2-8%) and high (8%) endemicity levels (6,7,8). In the Euro-Mediterranean countries, current median HBV endemicity levels are below 3% (9,10). There are insufficient data for the prevalence of chronic HBV infection in the Republic of North Macedonia (11). According to the data from the North Macedonian National Institute of Health, the modeled prevalence for chronic HBsAg carriers in the general population is 0.81% (12) but according to the European Centre for Disease Prevention and Control technical report (13) on the epidemiological assessment of hepatitis B and C among migrants in the European Union/European Economic Area countries, the HBsAg prevalence in migrants from North Macedonia is 3,29%. Mandatory vaccination against hepatitis B in children was introduced in the national immunization protocol of North Macedonia in 2004, and this vaccination has a high coverage of 91.3% with three doses. According the data from the registry of the patients with CHB infection that are being followed-up and treated at the university clinic for infectious diseases and febrile conditions, in Skopje, part of the medical faculty of the state university, and one of the two national centers for treatment of patients with chronic hepatitis, the majority of patients with chronic HBV infection have HBeAg-negative CHB, and only 9,7% of patients have HBeAg-positive CHB. Genotyping has not been done in patients with CHB in North Macedonia, but according to Hadziyannis (14), in the countries in the Mediterranean Basin and in the neighboring countries there is an overall predominance of HBV genotype D in more than 80% and even 90% of HBV infections (Figure 2). HBV genotype D characterizes with predominance of HBeAg-negative precore mutant CHB, which develops during the course of chronic HBV infection thus preventing the formation of HBeAg (15,16,17). Patients with HBeAg-negative CHB have periods of reactivation with a pattern of fluctuating HBV-DNA and aminotransferase levels and histologic signs of active hepatitis and may have a potentially severe and progressive course toward cirrhosis and development of HCC (14,16,18). Long-term prognosis is poorer among patients with HBeAg-negative CHB compared to patients with HBeAg-positive CHB (18,19). Sustained off-therapy responses are rare with interferon-based therapies (19), only in a small proportion of patients, and the majority of patients with HBeAg-negative CHB necessitate long-term oral antiviral therapy, mostly lifelong therapy, which improves patients' outcome but is associated with progressively increasing rates of viral resistance.

Therefore, appropriate use of effective therapy is an important issue in the management of this group of patients.

The Therapy of Patients with Chronic HBV Infection

In 2021, WHO estimated that 12% to 25% of people with CHB infection will require treatment, depending on the setting and eligibility criteria (2). Antiviral therapy improves survival and quality of life by preventing liver disease progression to cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, and death (4,5,20,21). The main endpoint of current treatment strategies is the induction of long-term suppression of HBV replication, and the loss of HBsAg is considered to be an optimal endpoint. Currently approved treatment options for CHB, peginterferon alpha-(PegIFN-α) and nucleos(t)ide analogues-NAs, do not offer a "complete cure"- clearance of covalently closed circular DNA and integrated HBV-DNA and rarely achieve a "functional cure" i.e. HBsAg loss. Eight NAs have been approved against HBV, of which the current recommended ones are entecavir and the two tenofovir prodrugs, disoproxil and alafenamide, with a high barrier to resistance, while in highly selected patients, an alternative treatment option is PegIFN (4,5,20,22,23).

The main advantage of PegIFN is the fixed duration of therapy and the chance for HBsAg seroconversion, but genotype D HBV patients have the lowest response rates, with only 20% achieving sustained control of viral replication (19,20,24). NAs inhibit HBV reverse transcriptase activity and therefore block HBV-DNA replication; they suppress viremia at clinically undetectable levels in up to 76% of HBeAg-positive and 93% of HBeAg-negative patients after one year of treatment. Their use is essentially lifelong for most patients, particularly those with HBeAg-negative CHB (20). Long-lasting, treatment-maintained suppression of HBV-DNA without resistance is achievable in most patients treated with entecavir or tenofovir (4,5,20,25).

Lamivudine, an oral NAs the first approved NA effective against HBV has very few side effects (25), but prolonged therapy results in high rates of viral resistance occurring in 14-32% of patients after 1 year of therapy, and in 60-70% of patients after 5 years, hence it is no longer widely used (26,27,28). Adefovir, an acyclic nucleotide analog initially used as monotherapy in patients with lamivudine resistance, but the development of resistance to adefovir was common, with inadequate control of viral replication (29).

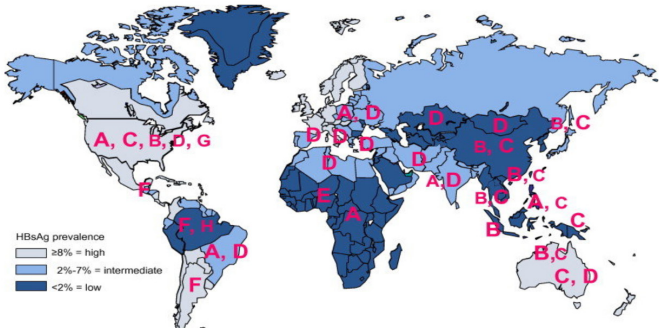

Figure 2. Geographical map displaying the levels of HBV endemicity in the world and the areas of predominance of the various HBV genotypes (14,17)

HBsAg: Hepatitis B surface antigen

Telbivudine is also a highly effective antiviral agent but has a very rapid emergence of resistance variants of HBV, 30% in 3 years. Lamivudine, adefovir, and telbivudine are no longer recommended as first-line therapies; however, they may still be widely prescribed in lower-middle income countries (4,5,20,25,26). Entecavir, a purine-derived NAs is a highly effective inhibitor of viral replication with few side effects. Long-term, minimum 3 years of entecavir therapy appears to result in the reversal of fibrosis and cirrhosis with improvement in liver histology. HBV drug resistance to entavir is extremely uncommon; it has been reported in only 1.2% of cases after 5 years. Entecavir is not the best choice of therapy for patients with established lamivudine resistance due to partial cross-resistance between lamivudine and entecavir and even given in a higher dose, 50% of such patients will develop entecavir resistance in 5 years (26). Entecavir is contraindicated in pregnancy and is not a good choice in young women who might be planning to or may accidentally become pregnant (30,31). Tenofovir disoproxil fumarate is an acyclic adenine nucleotide with potent activity against HBV and even after 8 years of follow-up of the patients, there was no tenofovir resistance registered (32). Tenofovir is the agent of choice for patients with lamivudine resistance because lamivudine and tenofovir have different mutational pathways to resistance and are highly effective in patients with prior adefovir resistance despite their similar resistance pathways, with 60-90% of patients receiving tenofovir having undetectable HBV-DNA after 1 year of therapy (29,33). Tenofovir alafenamide is a novel tenofovir prodrug with an improved safety profile. Tenofovir alafenamide is non-inferior to tenofovir disoproxil fumarate in both HBeAg-positive and HBeAg-negative CHB, and people treated with tenofovir alafenamide experienced smaller changes in bone mineral density and smaller declines in estimated glomerular filtration rate (34,35).

The Therapy of Patients with Chronic HBV Infection in North Macedonia

Republic of North Macedonia (Macedonia before 2019) is a country in Southeast Europe. It gained its independence in 1992 as one of the successor states of Yugoslavia and has a total area of 25,713 km^2 (9,928 sq mi). As of 2005 North Macedonia's unemployment rate was 37.2% and as of 2006, its poverty rate was 22% (36). The country's unemployment rate in the first quarter of 2015 decreased to 27.3% (37). North Macedonia has one of the highest shares of people struggling financially, with 72% of its citizens stating that they could manage on their household's income only "with difficulty" or "with great difficulty" (38). Census data from the last 2021 census show a population of 1,836,713 inhabitants (39) and North Macedonia Annual Household Income per Capita reached 2,627,562 USD in December 2021, compared with the previous value of 2,394.441 USD in Dec 2020 (40). The average monthly income in North Macedonia is 516.00 US Dollar per capita. In the USA, the figure is 5,911 US Dollar. However, the prices of consumer goods are also around 57.6% lower than in the USA, so when income and price levels are compared, the result is a more expensive life in North Macedonia than in the United States (41). The Republic of North Macedonia has a compulsory insurance-based health system with near universal coverage, and the current benefits package is considered to be very comprehensive. The Government and

the Ministry of Health provide the framework for operation and stewardship, and the Health Insurance Fund of North Macedonia is responsible for the collection of contributions, allocation of funds, and the supervision and contracting of providers. In the compulsory health insurance system, the funds generated by collecting contributions represent the main source of financing for the health sector. Co-payments by insured people and transfers from the state budget constitute additional sources of revenue, though rather small. Co-payments must be made by insured people for using health services and drugs (specified on a list) at all levels of care (42). The Health Insurance Fund established the Reference Price System for Positive Drug List (PDL) in 2008. This PDL has not been revised and expanded since 2011, and on this PDL only lamivudine is available through the co-payment system for people with CHB.

According to the data from one single center hospital, university clinic for infectious disease, from the registry of our patients with CHB, most patients are treated with NAs, namely with the first ever approved drug lamivudine, being the only drug on the PDL from the Insurance Fund of North Macedonia. A very small portion of patients, mostly with HBeAg-positive CHB that were treated with PegIFN, but except for very few who achieved HBeAg serotonversion and even fewer who achieved functional cure, the majority had to be treated with NAs. There is an increasing number of patients with CHB who have developed lamivudine resistance because of treatment longevity. Less than 15% of the patients with CHB are receiving tenofovir disoproxil fumarate mainly due to financial constraints. Namely, tenofovir is registered in North Macedonia, but it is not on the PDL, and the price for 1-month supply of the drug costs around 27% of the average monthly income in North Macedonia. Entecavir is also not on the PDL, and it has been registered only recently, the price for the drug has not been formed, and it is still not available on the market. Other drugs approved for the treatment of CHB such as adefovir and tenofovir alafanamid are not registered and therefore not available in North Macedonia.

A particular problem arises for patients who have developed resistance to lamivudine and who necessitate therapy with high barrier to resistance NAs. The drug resistance of entecavir is only 1% over 5 years in treatment-naive patients (4,5,43), but the rate of entecavir resistance could increase to 51% in lamivudine resistant patients because if primary lamivudine resistance mutations occur, compensatory resistance mutations to entecavir may arise even if primary lamivudine treatment is stopped (44). Therefore, entecavir is not the best treatment option after the development of lamivudine resistance in our patients because the majority of patients with CHB in North Macedonia are being or have been treated with lamivudine. Given the economic milieu of the country, it is more than obvious that therapy with tenofovir for the patients who have to be treated with this drug due to lamivudine resistance and have to buy it represents a significant monetary issue that undermines their already burdened domestic budget. Hence, it is necessary to raise the public, governmental, and policymakers' awareness about the management of patients with CHB and to put NAs with high resistance barriers on the PDL and to be covered by the North Macedonian Insurance Fund.

Conclusion

Republic of North Macedonia belongs to the countries with intermediate prevalence of chronic HBsAg carriage according to pooled data, and although routine immunization against hepatitis B has been implemented in the country since 2004 it has not shown its effect yet, seen by decreasing incidence and prevalence of both the acute and chronic form of HBV infection. Predominately, the patients in North Macedonia have HBeAg-negative CHB, and the only available drug which is on the PDL is lamivudine. According to the guidelines, treatment of patients with chronic HBV infection should be started with NAs with high resistance barrier to reduce the progression of the liver disease, but the prescription of tenofovir and entecavir, not being on the PDL, is limited due to financial constraints, whereas tenofovir alafenamide is not registered in North Macedonia. Entecavir resistance might be a clinical problem in antiviral treatment-experienced patients as are our patients, and if available, it should be reserved for treatment naïve patients. In our lamivudine - resistant patients, tenofovir is the agent of choice because lamivudine and tenofovir have different mutational pathways to resistance. Tenofovir monotherapy might be the optimal strategy for CHB patients in the Republic of North Macedonia, either treatment naïve or treatment experienced, and since cure rates are low, most patients will require therapy indefinitely. Effective antiviral treatment with universal vaccination should be implemented continuously to decrease the prevalence of chronic HBV infection in North Macedonia.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.D., Design: M.D., Data Collection or Processing: M.D., M.B., B.T., Analysis or Interpretation: M.D., M.B., B.T., Literature Search: M.D., M.B., B.T., Writing: M.D., M.B.

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