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Review

New pharmaceutical approaches in hepatitis B virus diagnosis and treatment

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ABSTRACT

The hepatitis B virus (HBV) is a deoxyribonucleic acid (DNA) virus that produces various antigens, against which the host develops antibodies. One of the most significant characteristics of HBV is its ability to form covalently closed circular DNA, allowing it to persist within cells. Millions of people worldwide are infected with HBV, resulting in many deaths due to severe complications. The hepatitis B virus can cause acute or chronic infections and lead to cirrhosis and liver cancer. Transmission routes include percutaneous, sexual, perinatal, and horizontal pathways. The treatment of HBV infection involves the use of interferons and nucleoside/nucleotide analogs. The most effective prevention method is the hepatitis B vaccine, which provides high protection. The prevalence of hepatitis B in Türkiye varies by geographic region. To prevent the spread of HBV, safe practices and vaccinations are of critical importance. This review addresses the characteristics of HBV, transmission routes, treatment methods, the importance of vaccination, and prevalence.

Keywords: Chronic HBV treatment, hepatitis B virus, liver infection.

Hepatitis B virus (HBV) belongs to the family *Hepadnaviridae* and is a deoxyribonucleic acid (DNA) virus with a viral genome consisting of 3200 nucleotides. Three viral antigens are synthesized by HBV: hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and hepatitis B core antigen (HBcAg). The host can produce antibodies against each of these three antigens, namely anti-HBs, anti-HBe, and anti-HBc, respectively.[1-4]

An important feature of HBV is its ability to form covalently closed circular DNA (cccDNA) during viral replication, which serves as a template for ribonucleic acid (RNA) copies. This cccDNA allows HBV to persist within hepatocytes, ensuring the continuity of virus production and contributing to its lifelong persistence, thus presenting a significant challenge for HBV treatment.[5-7]

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It is estimated that more than two billion people worldwide are infected with HBV, and 257 million people have chronic infections. Approximately 887,000 people die each year as a result of complications caused by chronic hepatitis B (CHB) infection.[8]

Hepatitis B was first described by Hippocrates around 450 BC; however, the actual discovery occurred in 1964 when Blumberg detected HBsAg (the Australia antigen) in the blood of an Australian patient.[9]

Hepatitis B can be either acute or chronic; if acute HBV infection lasts longer than six months, it becomes chronic. Chronic infection usually persists for a lifetime and can lead to cirrhosis, liver cancer, and even death in the long term.[10]

There are four primary routes of HBV transmission: percutaneous (parenteral) route, sexual transmission, perinatal (vertical) transmission (from an infected mother to her child during birth), and horizontal transmission.[10,11]

The natural course of chronic HBV infection is evaluated in four stages: HBeAg-positive chronic HBV infection, HBeAg-positive CHB, HBeAg-negative chronic HBV infection, and

HBeAg-negative CHB. However, not all stages may be observed in every patient.[12]

Diagnosis of HBV infection focuses on the detection of HBsAg. During the initial phase of infection, patients are seropositive for HBeAg. Hepatitis B e antigen indicates active viral replication and high infectivity. Chronic infection is characterized by the persistence of HBsAg for at least six months (with or without concurrent HBeAg). However, HBV-DNA is the most reliable indicator of viral replication.[13]

The main goal in the treatment of CHB is to prevent the progression of the disease to cirrhosis, decompensation, and liver failure, as well as the development of hepatocellular carcinoma (HCC), and liver-related mortality.[14]

Although the optimal treatment goal is HBsAg loss and seroconversion, the persistence of cccDNA within infected hepatocytes at the cellular level means that the infection will continue despite current antiviral treatment options. Therefore, if HBV replication is suppressed at low levels for an extended period, HBeAg seroconversion can be considered as the endpoint of treatment.[12]

Two classes of drugs are used for the treatment of CHB infections. The first is interferon, which is currently used in pegylated interferon (PegIFN), and the second is nucleoside or nucleotide/nucleoside analog (NA).[12]

The recent guidelines published by the World Health Organization (WHO), the European Association for the Study of the Liver (EASL), and the American Association for the Study of Liver Diseases recommend the use of entecavir (ETV), tenofovir disoproxil fumarate (TDF), and the recently introduced tenofovir alafenamide as the first-line treatment options due to their high resistance barrier and efficacy in suppressing the HBV. The most effective way to prevent hepatitis B is through hepatitis B vaccination. Since 1981, a hepatitis B vaccine has been available, which is 95% effective in preventing hepatitis B infection, chronic disease, and the development of liver cancer.[13]

Hepatitis B Virus Epidemiology

According to 2017 WHO data, it is estimated that more than two billion people worldwide are infected with HBV, and 257 million people have chronic infections. The majority of the 887,000 deaths attributed to hepatitis B in 2015 were found to be due to complications such as cirrhosis and HCC.[8]

Despite the availability of a reliable and effective vaccine, chronic HBV infection still affects approximately 240 million people globally, posing a significant global health burden. Numerous epidemiological and molecular studies have shown that CHB infection is the primary risk factor for the development of HCC. While chronic HBV infection is observed in about 5% of adults, this rate reaches up to 90% in neonatal infections. While HBV generally does not directly cause cytotoxic effects, it is believed to induce liver damage (fibrosis, cirrhosis, and HCC) in the presence of ongoing immune reactions and continuous inflammation in the liver. In the world, HBsAg prevalence is categorized into high (≥8%), high-intermediate (5-7%), low-intermediate (2-4%), or low (<2%) endemicity regions. Hepatitis B surface antigen positivity ranges from 0.1% to 20% globally. Areas with low prevalence (<2%) include Western Europe, the United States, and Canada.[10]

In these regions, the risk of lifelong infection is less than 20%. The infection is usually acquired during adulthood. In adolescents and young adults, sexual contact and sharing of needles among injecting drug users have been identified as the most significant transmission routes in these areas. However, infections acquired during the perinatal or early childhood period pose a significant risk for the development of HBV infection.[14,15]

Low-intermediate prevalence regions include Mediterranean countries, Japan, Central Asia, the Middle East, South America, Australia, and New Zealand, with a lifelong infection risk of 20-60%.[10]

Low-intermediate prevalence regions, including our country, exhibit characteristics of both regions in terms of transmission. Additionally, in this group, it has been determined that unsafe healthcare practices are also a significant mode of transmission.[15]

Our country is located among the low-intermediate endemic regions, and it is estimated that approximately 3.5 million

people are infected with HBV.[16] Hepatitis B virus prevalence varies by geographical region within the country, with carrier rates reported as approximately 6% in the western regions, while in the eastern and southeastern regions, it ranges between 12.5% and 14.3%.[17] According to a report on hepatitis B prepared by the European Centre for Disease Prevention and Control in September 2010, the prevalence of HBV infection in the general population in Türkiye was found to be between 2-8%. Hepatitis B surface antigen positivity was reported as 64% in cirrhotic patients and 54% in HCC cases. According to this report, Türkiye is one of the countries with the highest prevalence of hepatitis B compared to European countries.[16]

Transmission Routes of Hepatitis B Virus

Hepatitis B virus has four main transmission routes;

I. Percutaneous (parenteral) transmission: It is one of the most important transmission routes in HBV infection. It occurs through contact with infected blood and body fluids. It is an effective mode of HBV transmission and can pose a risk of up to 30% in individuals without post-exposure prophylaxis or proper vaccination. Parenteral drug use, contaminated needle injuries, dialysis, getting tattoos, ear piercings, wearing earrings, and acupuncture are among the most significant examples of this type of transmission. The virus can survive outside the human body for more than seven days, so infected toothbrushes and razors can also serve as sources of transmission.

II. Sexual contact (semen and vaginal secretions): Sexual transmission of HBV can occur, especially in men who have sex with men, individuals with multiple sexual partners, unvaccinated men who have sex with sex workers, or sexual partners of HBV carriers. Sexual transmission is most commonly observed in low-prevalence areas.

III. Vertical transmission from an infected mother to newborn (perinatal-vertical): Transmission from the mother to the baby can occur during pregnancy, childbirth, and/or after birth. Babies born to HBeAg-positive mothers are infected in 70-90% of cases, and 90% of these infections become chronic. Babies born to HBeAg-negative mothers are infected in 10-20% of cases, and 40-70% of these infections become chronic. Although a small amount of HBV has been detected in breast milk, there is no evidence to suggest that hepatitis B is transmitted through breast milk.

IV. Horizontal transmission: This includes the transmission of the virus within households, family members, and from child to child through small cracks in the skin or mucous membranes. Although the viral load in saliva and semen is lower compared to serum, infectious virions are continuously found in saliva and semen. Transmission has been observed through close contact such as between mother and child, siblings, and close friends, as well as through sharing of common items such as toys, utensils, and razors, which may lead to small skin cuts or bites.[11-18]

Hepatitis B Virus Life Cycle

The hepatitis B virus binds to the hepatocyte membrane through the sodium taurocholate cotransporting polypeptide, detaching from its envelope, and entering the cell cytoplasm within the nucleocapsid. Inside the nucleocapsid, there is relaxed circular DNA (rcDNA). The rcDNA moves towards the cell nucleus, where it converts into cccDNA upon entering the nucleus. Within the nucleus, cccDNA undergoes transcription, leading to the synthesis of subgenomic and pregenomic RNAs, which will be used in the synthesis of viral proteins, and they are exported to the cytoplasm. In the cytoplasm, pregenomic RNAs are encapsidated, and negative and positive strand DNAs are synthesized via reverse transcription, resulting in the formation of rcDNA again. This structure inside the nucleocapsid is either transported back to the nucleus for the formation of cccDNA or packaged with the Golgi apparatus to be released outside the cell to infect other cells.[17,18]

The Clinical Stages of Hepatitis B Infection

Hepatitis B infection is clinically divided into four stages based on viral replication and transaminase levels: the immune tolerant phase, the immune response (clearance) phase, the inactive chronic hepatitis phase, and the reactivation phase. However, in the EASL 2017 guidelines, the natural course of chronic hepatitis

has been divided into five phases based on the presence of HBeAg positivity and the presence of hepatitis symptoms. It should be noted that these five phases should not be perceived as consecutive periods, as in the previous definition.

Phase 1: HBeAg-positive chronic HBV infection (immune tolerant phase)

Phase 2: HBeAg-positive chronic hepatitis B

Phase 3: HBeAg-negative chronic HBV infection

Phase 4: HBeAg-negative chronic hepatitis

Phase 5: Hepatitis B surface antigen-negative phase; in this phase, HBsAg is negative while anti-HBc is positive. Hepatitis B surface antibody (anti-HBs) can be positive or negative. Hepatitis B virus DNA is generally negative, but cccDNA is detected in the liver. This phase is known as "occult HBV infection." If HBsAg loss occurs before the development of cirrhosis, the risk of decompensation and HCC development is negligible. However, if HBsAg loss occurs after the development of cirrhosis, these patients should continue to be monitored for HCC.[18]

TREATMENT OF CHRONIC HEPATITIS B

This virus, which infects approximately 240 million people worldwide, carries a risk of developing cirrhosis, hepatic decompensation, and HCC in 15-40% of infected patients. The goal of treatment is to suppress viral replication and prevent the occurrence of these complications.[15,16,19]

Treatment indications

When deciding on treatment for a patient with HBV infection, factors such as the patient's age, comorbidities, family history of HCC and cirrhosis, and the presence of extrahepatic manifestations should be taken into account. Serum HBV DNA levels, serum alanine aminotransferase (ALT) levels, and the extent of liver disease are the most important criteria in making this decision. In a patient without liver cirrhosis, HBV DNA >2,000 IU/mL, ALT >40 IU/mL, and moderate necroinflammation and/or moderate fibrosis as determined by liver biopsy require treatment decision. Although liver biopsy provides additional information about liver histology, it usually does not change the treatment decision. For this purpose, the evaluation of liver fibrosis using non-invasive methods is considered a useful approach in making treatment decisions.[17-19]

Drugs Used in Hepatitis B Virus Treatment

Interferon treatment

Interferon treatment affects various stages of the HBV life cycle, including entry of the virus into the cell, virion uncoating, DNA transcription, RNA translation, and assembly of viral particles. Although IFN treatment is generally a safe approach, inappropriate patient selection can lead to consequences ranging from hepatitis to hepatic failure. Patients with signs of decompensation in cirrhosis, portal hypertension, autoimmune diseases, severe leukopenia and/or thrombocytopenia, serious cardiopulmonary diseases, and major depression are not suitable candidates for IFN treatment. In HBV infections, pegylated interferon is preferred, with pegylated interferon alfa-2a 180 μg administered subcutaneously once a week for 48 weeks being the recommended dosage and duration of treatment. It can be used in cases of mild-to-moderate hepatitis and compensated cirrhosis without portal hypertension. The response rate to treatment after 12 months in HBeAg-positive CHB patients is approximately 20-30%. Hepatitis B e antigen loss is typically observed within the first six months in HBeAg-positive patients. The proportion of patients who achieve both HBeAg loss and HBV DNA <2000 IU/mL is 23%.[19]

Oral antivirals-nucleoside and nucleotide analogs

Nucleoside/nucleotide analogs resemble natural nucleosides/nucleotides and act by inhibiting the HBV polymerase enzyme. The first drug to be introduced from this group was lamivudine (LAM), which effectively suppresses viral replication and reduces the risk of developing complications associated with HBV. However, the emergence of high rates of resistance with long-term use and the emergence of new and effective antivirals have pushed LAM down the preference rankings. Following LAM, the drugs that have been introduced are adefovir (ADV),

telbivudine (LdT), ETV, and TDF. Entecavir and TDF are the preferred drugs due to their high resistance barrier and low side effect profiles. Although the side effects of NAs are minimal, mitochondrial toxicity, defined as a group effect, is one of the most important side effects. These drugs can cause mitochondrial toxicity through inhibition of human mitochondrial polymerase-gamma.[20,21]

Damage to the mitochondria disrupts the respiratory chain within the cell, preventing reactions that require oxidative phosphorylation, such as adenosine triphosphate and DNA synthesis, from occurring. Another consequence of mitochondrial polymerase-gamma inhibition is the increase in reactive oxygen radicals, which can damage the cell.[22-24]

The clinical manifestations of mitochondrial toxicity include hematological disorders, peripheral neuropathy, muscle problems, cardiac myopathy, pancreatitis, liver failure, and lactic acidosis.[23-25]

Lamivudine

Lamivudine, a cytidine analog, is phosphorylated to its active form by the enzyme deoxycytidine kinase within the cell. In its active form, it competitively inhibits viral reverse transcriptase, thereby inhibiting reverse transcriptases and terminating the extension of the viral DNA chain. In patients with normal kidney function, the daily dose is 100 mg. While lamivudine has a favorable side effect profile, its prolonged use is limited by the development of resistance to the drug, leading to virological and biochemical flares.[20-27]

The most significant serious side effect is hepatitis flare due to early LAM resistance, leading to hepatic decompensation. Creatine kinase and ALT elevations thought to result from mitochondrial toxicity, a group effect of NAs, have spontaneously resolved in most cases without drug discontinuation, although severe elevations have necessitated cessation of the drug, leading to rapid resolution of clinical and laboratory values in most cases.[28]

Telbivudine

Telbivudine is a thymidine nucleoside analog that provides more potent viral inhibition compared to LAM and ADV; however, the development of high resistance to the drug has limited its use.[20] The most common side effects observed in patients using LdT are upper respiratory tract infection (URTI), nasopharyngitis, fatigue, and headache. Although CK elevation is frequently observed, it is generally asymptomatic and resolves spontaneously. Although the exact mechanism behind the occurrence of telbivudine-related side effects is not fully understood, it is believed that mitochondrial damage leads to a decrease in energy production and an increase in oxygen radicals, resulting in symptoms associated with tissues requiring high energy demands such as the nervous system, heart, and muscle tissue. In addition to the side effects associated with the use of LdT alone, the effect of adding LdT to combination therapies on side effects has also been evaluated. While combining LdT with LAM does not lead to additional side effects, combining it with interferon has been associated with a 17% incidence of peripheral neuropathy.[20-29]

Adefovir dipivoxil

Adefovir is a prodrug of a nucleotide analog. Due to its high resistance rates, its use has been in the form of adding ADV to treatment in cases resistant to LAM. At a dose of 10 mg/day used in the treatment of chronic HBV, side effects were found to be similar to placebo.[30,31]

The most common side effects include pharyngitis, fatigue, headache, abdominal pain, nausea, and flu-like symptoms.[30]

Entecavir

Entecavir is a guanosine nucleoside analog used at a dose of 0.5 mg in naive patients and 1 mg/day in LAM-resistant patients. Since it inhibits viral replication in three stages, the risk of drug resistance development is low. The side effects associated with ETV are not dose-dependent, and side effects occurring at doses of 0.5 mg and 1 mg are similar. The most common side effects include headache, URTI, cough, nasopharyngitis, weakness, dizziness, and upper abdominal pain. Most side effects are mild and do not require discontinuation of the medication.

Entecavir is considered the safest NAs in terms of mitochondrial toxicity. Combining ETV with

other antiviral treatments has not been observed to increase the risk of toxicity. Although cases of ETV-related myopathy and peripheral neuropathy have been reported, they are very rare side effects.[32,33]

Tenofovir

Tenofovir disoproxil fumarate is a prodrug that becomes active through hydrolysis and phosphorylation inside the cell, transforming into a nucleotide analog. It was approved for human immunodeficiency virus (HIV) treatment in 2001 and received approval from the Food and Drug Administration for HBV treatment in 2008. Due to its low incidence of identified drug resistance and its low side effect profile at the doses used for HBV treatment (245 mg/day), it is recommended as the preferred drug in current practice.[34]

The most common side effects include headache, nasopharyngitis, back pain, and nausea. Long-term treatment with TDF in HIV patients has been associated with osteomalacia and decreased bone mineral density. The decrease in bone mineral density is interpreted as a result of decreased osteoblast activity and increased osteoclast activity due to HIV infection. However, subsequent publications have shown that TDF can alter osteoblast gene expression and functions, thus affecting bone mineral density.[35]

In conclusion, interactions between organizations focused on HBV treatment and those implementing chemotherapy and biological therapy are recommended, aiming to organize joint educational meetings and raise awareness about HBV through such programs. Ultimately, humanity continues to combat HBV. This battle will increasingly turn in our favor as our knowledge about HBV expands. The introduction of drugs that target cccDNA and affect the immune system holds the greatest promise for the future.

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REFERENCES

1. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: A systematic review of data published between 1965 and 2013. Lancet 2015;386:1546-55. doi: 10.1016/S0140-6736(15)61412-X.
2. World Health Organization. Global Hepatitis Report. 2017. Available at: http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf.
3. Akhan S, Aynıoğlu A, Çağatay A, Gönen İ, Günal Ö, Kaynar T, et al. Kronik hepatit B virusu infeksiyonunun yönetimi: Türk klinik mikrobiyoloji ve infeksiyon hastalıkları derneği viral hepatit çalışma grubu uzlaşı raporu. Klimik Dergisi 2014;27:2-18.
4. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001;344:495-500. doi: 10.1056/NEJM200102153440706.
5. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22:696-9. doi: 10.1016/0168-8278(95)80226-6.
6. Kramvis A. The clinical implications of hepatitis B virus genotypes and HBeAg in pediatrics. Rev Med Virol 2016;26:285-303. doi: 10.1002/rmv.1885.
7. Valaydon ZS, Locarnini SA. The virological aspects of hepatitis B. Best Pract Res Clin Gastroenterol 2017;31:257-64. doi: 10.1016/j.bpg.2017.04.013.
8. World Health Organization [internet]. 2018 Available at: http://www.who.int/mediacentre/factsheets/fs204/en/ [Accessed: 30.04.2018].
9. Mahoney FJ. Update on diagnosis, management, and prevention of hepatitis B virus infection. Clin Microbiol Rev 1999;12:351-66. doi: 10.1128/CMR.12.2.351.
10. Mauss S, Berg T, Rockstroh J, Sarrazin C, Wedemeyer H. Hepatology - A clinical textbook. 7th ed. Germany: Druckerei Heinrich GmbH; 2016.
11. Kwon SY, Lee CH. Epidemiology and prevention of hepatitis B virus infection. Korean J Hepatol 2011;17:87-95. doi: 10.3350/kjhep.2011.17.2.87.
12. European Association for the Study of the Liver. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-98. doi: 10.1016/j.jhep.2017.03.021.
13. Krajden M, McNabb G, Petric M. The laboratory diagnosis of hepatitis B virus. Can J Infect Dis Med Microbiol 2005;16:65-72. doi: 10.1155/2005/450574.
14. Wu CY, Lin JT, Ho HJ, Su CW, Lee TY, Wang SY, et al. Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B: A nationwide cohort study. Gastroenterology 2014;147:143-51.e5. doi: 10.1053/j.gastro.2014.03.048.
15. Valsamakis A. Molecular testing in the diagnosis and management of chronic hepatitis B. Clin Microbiol Rev 2007;20:426-39, table of contents. doi: 10.1128/CMR.00009-07.

16. European Centre for Disease Prevention and Control. Hepatitis B and C in the EU neighbourhood: prevalence, burden of disease and screening policies, Stockholm: ECDC; 2010.
17. Leblebicioglu H, Eroglu C; Members of the Hepatitis Study Group. Acute hepatitis B virus infection in Turkey: Epidemiology and genotype distribution. Clin Microbiol Infect 2004;10:537-41. doi: 10.1111/j.1469-0691.2004.00871.x.
18. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-98. doi: 10.1016/j.jhep.2017.03.021.
19. Sonneveld MJ, Hansen BE, Piratvisuth T, Jia JD, Zeuzem S, Gane E, et al. Response-guided peginterferon therapy in hepatitis B e antigen-positive chronic hepatitis B using serum hepatitis B surface antigen levels. Hepatology 2013;58:872-80. doi: 10.1002/hep.26436.
20. Fung J, Lai CL, Seto WK, Yuen MF. Nucleoside/nucleotide analogues in the treatment of chronic hepatitis B. J Antimicrob Chemother 2011;66:2715-25. doi: 10.1093/jac/dkr388.
21. Wolters LM, Niesters HG, de Man RA. Nucleoside analogues for chronic hepatitis B. Eur J Gastroenterol Hepatol 2001;13:1499-506. doi: 10.1097/00042737-200112000-00016.
22. Fung J, Seto WK, Lai CL, Yuen MF. Extrahepatic effects of nucleoside and nucleotide analogues in chronic hepatitis B treatment. J Gastroenterol Hepatol 2014;29:428-34. doi: 10.1111/jgh.12499.
23. Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. Hepatology 2009;49(5 Suppl):S185-95. doi: 10.1002/hep.22885.
24. Marcellin P, Wursthorn K, Wedemeyer H, Chuang WL, Lau G, Avila C, et al. Telbivudine plus pegylated interferon alfa-2a in a randomized study in chronic hepatitis B is associated with an unexpected high rate of peripheral neuropathy. J Hepatol 2015;62:41-7. doi: 10.1016/j.jhep.2014.08.021.
25. Martin JL, Brown CE, Matthews-Davis N, Reardon JE. Effects of antiviral nucleoside analogs on human DNA polymerases and mitochondrial DNA synthesis. Antimicrob Agents Chemother 1994;38:2743-9. doi: 10.1128/AAC.38.12.2743.
26. Pala HG, Erbas O, Pala EE, Artunc Ulkumen B, Akman L, Akman T, et al. The effects of sunitinib on endometriosis. J Obstet Gynaecol 2015;35:183-7. doi: 10.3109/01443615.2014.941345.
27. Aykan K, Altuntaş İ, Erbaş O. DNA repair mechanisms: DNA repair defects and related diseases. D J Med Sci 2022;8:130-40. doi: 10.5606/fng.btd.2022.120.
28. Adani GL, Baccarani U, Risaliti A, Bresadola F, Della Rocca G, Viale P. Rhabdomyolysis due to Lamivudine administration in a liver transplant recipient. Am J Transplant 2005;5:634. doi: 10.1111/j.1600-6143.2005.00691.x.
29. Lai CL, Leung N, Teo EK, Tong M, Wong F, Hann HW, et al. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology 2005;129:528-36. doi: 10.1016/j.gastro.2005.05.053.
30. Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med 2003;348:808-16. doi: 10.1056/NEJMoa020681.
31. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. N Engl J Med 2003;348:800-7. doi: 10.1056/NEJMoa021812.
32. Matthews SJ. Entecavir for the treatment of chronic hepatitis B virus infection. Clin Ther 2006;28:184-203. doi: 10.1016/j.clinthera.2006.02.012.
33. Suzuki F, Toyoda J, Katano Y, Sata M, Moriyama M, Imazeki F, et al. Efficacy and safety of entecavir in lamivudine-refractory patients with chronic hepatitis B: Randomized controlled trial in Japanese patients. J Gastroenterol Hepatol 2008;23:1320-6. doi: 10.1111/j.1440-1746.2008.05455.x.
34. Lok AS, McMahon BJ. Chronic hepatitis B: Update 2009. Hepatology 2009;50:661-2. doi: 10.1002/hep.23190.
35. Gill US, Zissimopoulos A, Al-Shamma S, Burke K, McPhail MJ, Barr DA, et al. Assessment of bone mineral density in tenofovir-treated patients with chronic hepatitis B: Can the fracture risk assessment tool identify those at greatest risk? J Infect Dis 2015;211:374-82. doi: 10.1093/infdis/jiu471.