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Demographics of the chronic HBV infection suitable for antiviral treatment – 20 years of experience in a single Bulgarian centre

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Abstract

We present data from a single hepatology centre in Bulgaria which started its activity in the late 1990s. Currently 427 patients are treated with nucleotide or nucleoside analogues (NUCs), 104 of whom with liver cirrhosis. The majority - 60% of the patients – are diagnosed with chronic hepatitis B infection (both chronic hepatitis and liver cirrhosis) after 2000. The females are less than 1/3 of the patients. HBe antigen carriers are 86 of the patients with chronic hepatitis – 26% and 9 of those with liver cirrhosis – 8.5%.

The chronic viral infection was diagnosed on average at the age of 45.7±13.9 years for the patients with liver cirrhosis (44.6±13.5 years for males and 48.0±14.7 years for females). For those with chronic hepatitis B the age at the diagnosis was 38.3±14.1 (37.7±14.4 years for the males and 39.8±14 years for the females).

Only 25% of the patients are original from Sofia. The remaining 75% are from other parts of the country, mainly from Southern (32%) and Western Bulgaria (19%).

This group of patients gives an idea about the gender and age distribution at the time of the detection of the chronic hepatitis B viral infection in Bulgaria. Women who are less than 1/3 of the patients are

slightly older than the men. Most patients were diagnosed during the last decade, which corresponds to the improved healthcare in Bulgaria.This group of patients gives an idea about the gender and age distribution at the time of the detection of the chronic hepatitis B viral infection in Bulgaria. Women who are less than 1/3 of the patients are slightly older than the men. Most patients were diagnosed during the last decade, which corresponds to the improved healthcare in Bulgaria.

Keywords: hepatitis B, liver cirrhosis, polymerase inhibitors, interferon alpha, Bulgaria.

Introduction

One third of the world's population has a serologically proven past or present infection with the hepatitis B virus. Globally, HBsAg carriers are 350-400 million people (1). The incidence of HBV infection in Bulgaria is intermediate – 3.9 %. (2, 3). A study held in Sofia reports a lower rate – 2.2 % of the blood donors in the capital city are HBsAg positive (4). Mortality in HBsAg-positive patients is higher than in the general population, 12.6 times due to chronic liver disease, 15.9 times from hepatocellular carcinoma and 8.6 times due to non-Hodgkin's lymphoma (5). Despite the presence of an effective vaccine and powerful antiviral therapy, the overall burden of hepatitis B-related illnesses is still significant (6).

With the diagnosis of chronic HBV infection, the progression of the disease may be delayed or stopped. There are two main groups of antiviral drugs used in chronic hepatitis B infection: interferon alpha (classic or pegylated) and polymerase inhibitors (NUCs). Approved for the treatment of chronic hepatitis B infection in Bulgaria are the nucleoside analogues Lamivudine, Telbivudine, Entecavir and the nucleotide analogues Adefovir and Tenofovir. In the last years the first line of treatment are Tenofovir and Entecavir.

Despite its low genetic barrier and up to 70% of resistance at the 5th year of therapy lamivudine is still used as the first choice of therapy in selected patients (7) because of its low cost and availability.

Materials & Methods

We present data from a single hepatology centre in Bulgaria which started its activity in the late 1990s. Currently 427 patients are treated with NUC, 104 of whom with liver cirrhosis. The majority - 60% of the patients – are diagnosed with chronic hepatitis B infection (both chronic hepatitis and liver cirrhosis) after 2000. The females are less than 1/3 (123 of the patients). HBe antigen carriers are 86 of the patients with chronic hepatitis – 26% and 9 of those with liver cirrhosis – 8.5%. Patients were treated with lamivudine 100 mg (ZeffixTM, GlaxoSmithKline), telbivudine 600 mg (SebivoTM, Novartis), tenofovir disoproxil 245 mg (VireadTM, Gilead) or entecavir 0.5 mg (BaracludeTM, Bristol-Myers Squibb). Serum HBV DNA levels were measured by LightCycler real time polymerase chain reaction assay (PCR) (Roche Diagnostics). Results are presented as the mean±SD, counts, and percentages.

Results

The chronic viral infection was diagnosed on average at the age of 45.7±13.9 years for the patients with liver cirrhosis (44.6±13.5 years for males and 48.0±14.7 years for females). For those with chronic hepatitis B the age at the diagnosis was 38.3±14.1 (37.7±14.4 years for the males and 39.8±14 years for the females). 30 and 28% of the patients diagnosed with liver cirrhosis and chronic hepatitis B respectively are female. Most of the patients (62%) were diagnosed after 2005 (table 1 and 2).

Table 1. All patients with chronic hepatitis B infection – year of HBsAg detection according to the medical history

Diagnosis		Patients	
from	to	Number of patients	%
2011	2015	154	36
2006	2010	110	26
2001	2005	60	14
1996	2000	45	11
1991	1995	25	6
	Before 1990	33	8

Table 2. Patients with chronic hepatitis B infection (at the stage of liver cirrhosis) – year of HBsAg detection according to the medical history

Diagnosis		Patients	
from	to	Number of patients	%
2011	2015	37	35.6
2006	2010	27	26
2001	2005	11	10.6
1996	2000	13	12.5
1991	1995	8	7.7
	Before 1990	8	7.7

Only 25% of the patients originate from the capital city Sofia. The remaining 75% are from other parts of the country, mainly from Southern (32%) and from Western Bulgaria (19%) (table 3).

Table 3. Patient's origins

Region	Number of patients (%)	Number of patients with liver cirrhosis	Number of patients with CHB
Sofia	108 (25.3)	20	88
Northern Bulgaria	72 (16.8)	17	55
Southern Bulgaria	136 (31.9)	40	96
Eastern Bulgaria	28 (6.6)	7	21
Western Bulgaria	83 (19.4)	21	62
Total	427	105	322

336 patients had a histological verification of the disease and started an antiviral treatment with NUCs (within a National Health Insurance Fund program or a clinical trial) within the first two years from the detection of HBsAg.

32 patients had a preceding Interferon alpha treatment and needed a NUC therapy on average 9.1±4.5 years after the first detection of HBsAg. 59 (14%) of all the patients had no proper diagnosis and no antiviral treatment at all for 12.0±9.3 years.

Patients detected before 2010 had a delay of 13.6 years, from 2010 to 2015 – 11.3 years before starting a treatment. HBV DNA was lower in the patients previously treated with Interferon (1.3E+08±2.6E+08 cp/ml) compared with those who had no antiviral therapy (5.6E+08±1.4E+09 cp/ml).

Discussion

Chronic hepatitis B infection has many different presentations. Patients without clinical symptoms might not be addressed in a timely manner to a specialist. This could be the reason 14% of the patients in our group had a late verification and treatment. 70% of the patients with acute hepatitis B and 100% with chronic hepatitis B in Bulgaria are genotype D (4, 8) and are expected to have a higher rate of mutations, lower rate of virological response and faster progression to liver cirrhosis and hepatocellular carcinoma. The expected five-year progression from chronic hepatitis to liver cirrhosis is 10-20%, from compensated to decompensated cirrhosis 20-30%, from compensated cirrhosis to hepatocellular carcinoma 5-15% (9, 10). The risk of death from complications of the liver disease is 40-50% in men and 15% in females (11). Nowadays the progression of the disease may be delayed or stopped. There are two main groups of drugs which are available: interferon alpha (classic or pegylated) and polymerase inhibitors (nucleotide and nucleoside analogues) (12, 13). Patients with liver cirrhosis are candidates for treatment regardless of the viral load. Those with decompensated liver cirrhosis are not indicated for treatment with interferon. These patients require a long-term treatment with polymerase inhibitors (NUCs). A significant effort is made last years to diagnose and evaluate patients for treatment faster.

Conclusion

This group of patients gives an idea of the demography of the chronic hepatitis B viral infection in Bulgaria. HBV was recognized at the age of 46 years for the patients with liver cirrhosis and for those with chronic hepatitis the age at the diagnosis was 38. Women are less than men - 1/3 of the patients and are slightly older at the time of the detection of the disease. 24 % of the patients are diagnosed at the stage of liver cirrhosis. HBe antigen positive are carriers are 26% of the patients with chronic hepatitis and 8.5% of those with liver cirrhosis. Most patients were diagnosed during the last decade and are referred to treatment sooner which corresponds to the improved healthcare in Bulgaria.

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