CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

DOI: 10.5152/cjms.2019.817

Outcomes of Chronic Hepatitis B Virus Infection in Children: A 20-Year Follow-up

Nafiye Urgancı[1], Derya Kalyoncu[2,3]

[1]Department of Pediatric gastroenterology, Şişli Hamidiye Etfal Training and Research Hospital, İstabul, Turkey
[2]Department of Pediatrics, Şişli Hamidiye Etfal Training and Research Hospital, İstabul, Turkey
[3]Department of Pediatrics, İstinye State Hospital, İstanbul, Turkey

ORCID IDs of the authors: N.U. 0000-0003-4854-507X; D.K. 0000-0001-8449-7621.

Cite this article as: Urgancı N, Kalyoncu D. Outcomes of Chronic Hepatitis B Virus Infection in Children: A 20-Year Follow-up. Cyprus J Med Sci 2019; 4(2): 77-83.

BACKGROUND/AIMS
The aim of the present study was to evaluate seroconversion rates in children with chronic hepatitis B (CHB) infection and determine the factors influencing the natural course of liver diseases.

MATERIAL and METHODS
A total of 458 hepatitis B surface antigen (HBsAg)-positive patients aged 0.75–17 years were tested for hepatitis markers, liver function tests, and hepatitis B virus (HBV) DNA levels at baseline and periodically at every 3 months following recruitment. Patients with CHB (n=321) were divided into two groups: treated and untreated patients. The seroconversion rates between the two groups were compared, and their relationship with age, sex, vaccination status, coinfections, aminotransferases, HBV DNA levels, and cirrhosis was determined.

RESULTS
Hepatitis B e antigen (HBeAg) seroconversion rates were 30 in 97 patients 30/97 (30.9%) in untreated patients and 67/147 (45.5%) in treated patients (p=0.023). HBsAg seroconversion rates were 10/174 (5.7%) in untreated patients and 16/147 (10.8%) in treated patients (p=0.10). No significant difference was observed in HBeAg and HBsAg seroconversion times between the two groups (p>0.05).

CONCLUSION
In our study, although the HBeAg seroconversion rate was significantly higher in treated patients than in untreated patients, the HBsAg seroconversion rate was not different between the groups.

Keywords: Children, chronic hepatitis B, cirrhosis, HBsAg, HBeAg, outcome

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a major cause of liver diseases associated with the development of cirrhosis and hepatocellular carcinoma (HCC). The natural course of HBV infection is greatly influenced by the age of the individuals at infection, host immune response to the virus, and the level of HBV replication (1). It The natural course of HBV infection comprises four phases: immune tolerance, immune clearance [hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB)], low or non-replication (inactive carrier state), and reactivation (HBeAg-negative CHB) (1-3).

The risk factors associated with the loss of hepatitis B surface antigen (HBsAg) and/or HBeAg that can occur spontaneously or following treatment and the development of progressive liver inflammation, fibrosis, and cirrhosis remain unclear. Given that it is not certain that treatment with interferon (IFN) increases seroconversion rates and improves prognosis, the benefits of treatment (IFN, lamivudine) have not been established (4-6). The risk for cirrhosis and HCC is low; therefore, treatment is not recommended because of the development of viral resistance in carriers who are in the immune tolerance phase (6). However, children with CHB infection would require regular screening for the progression of infection to cirrhosis and HCC because some of them will subsequently have flares of hepatitis and develop HBeAg-positive immune active hepatitis or HBeAg-negative active hepatitis (5, 6).

Corresponding Author: Derya Kalyoncu
E-mail: deryakaly@hotmail.com

Received: 22.01.2019
Accepted: 31.03.2019

The present study aimed to evaluate seroconversion rates in children with CHB infection and determine the factors influencing the natural course of liver diseases.

MATERIAL and METHODS

A total of 458 HBsAg-positive children who were admitted to the Division of Pediatric Gastroenterology of Sisli Hamidiye Etfal Training and Research Hospital (Istanbul, Turkey) between 1998 and 2018 were retrospectively evaluated. Data on vaccination status, duration of HBsAg positivity, type of onset (acute or chronic), mode of transmission, concomitant hepatitis D virus (HDV) and/or hepatitis C virus (HCV) positivity, and physical examination signs (hepatomegaly, splenomegaly, and ascites) were obtained.

Complete blood count, biochemical tests, coagulation tests, HBsAg, antibody to hepatitis B surface antigen (anti-HBs), total antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis B e antigen (anti-HBeAg), anti-HCV, anti-HDV, and antibody to human immunodeficiency virus were examined in all patients using commercially available enzyme-linked immunoassays (Cobas Core, Roche Diagnostics, Pleasanton, CA, USA). HBV DNA and HCV RNA levels were measured using quantitative real-time polymerase chain reaction (COBAS TaqMan 48; Roche Diagnostics, Pleasanton, CA, USA). Liver biopsy was performed according to the Menghini technique. The stage and grade of liver involvement were scored according to Knodell's hepatic activity index (HAI) (7) in all treated patients. Children were followed up by testing HBeAg, HBsAg, HBV DNA, and liver function every 3 months for the first year and then annually. The study was approved by the Ethics Committee of the institution. Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki ' Ethical Principles for Medical Research Involving Human Subjects' (amended in October 2013).Informed consents were obtained from all the parents of the children before biopsy and other procedures.

Patients whose alanine aminotransferase (ALT) and aspartate aminotransferase levels were three times the upper normal limits at admission were regarded as acute onset patients. Patients whose HBsAg continued to be positive for >6 months, indicating chronic HBV infection, were included in the study. A total of 44 (9%) patients who developed seroconversion during the first 6 months were regarded as acute hepatitis B infection and those with fulminant hepatitis were excluded from the study. Of the 414 HBeAg-positive children, 93 were excluded because of incomplete patient data or were lost to follow-up.

Inactive carriers were defined as HBeAg negativity, anti-HBe, undetectable or low levels of HBV DNA (<2000 IU/mL or 10^4 copies/mL), persistent normal levels of ALT, and inactive liver histology (2, 4). HBeAg-negative chronic hepatitis (mutant HBV infection/precore or core promoter mutant) is defined as HBeAg negativity with anti-HBe positivity, detectable serum HBV DNA levels (2000–20 million IU/mL or 10^4–10^8 copies/mL), increased ALT, and moderate or severe necroinflammation with variable amounts of fibrosis on liver biopsy (2).

HBeAg seroconversion was defined as loss of HBeAg and gain of anti-HBe antibody occurring either spontaneously or following treatment. HBsAg seroconversion was defined as loss of HBsAg and gain of anti-HBsAg antibody. Reactivation was defined as an increase in ALT (more than twice the upper normal limit) with the reappearance of HBV DNA, with or without reversion to HBeAg.

During follow-up, patients whose HBsAg, HBeAg, and HBV DNA positivity persisted for >6 months, aminotransferase levels were twice the upper normal limit, who had liver biopsy, and in whom the other causes of liver diseases were excluded were started on treatment. Patients were treated with IFN alpha-2a or IFN alpha-2b (at a dose of 3–5 MU/m^2 three times a week for 6 months, subcutaneously) alone or in combination with lamivudine (4 mg/kg/day once daily for 12 months, orally). Response to treatment was defined as HBV DNA undetectability, loss of HBeAg with seroconversion to anti-HBe, and ALT normalization (ALT ≤1× upper normal limit).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 11.5 (SPSS Inc.; Chicago, IL, USA) software. All results are expressed as mean±SD. Statistical comparisons were made using the unpaired Student's t-test and Pearson correlation test. Qualitative variables were analyzed using Fisher's exact and chi-square tests. A p value of <0.05 was considered statistically significant.

RESULTS

The age of 321 patients with CHB of the 458 HBsAg-positive patients ranged from 0.75 to 17 (8.99±3.75) years, and the male-to-female ratio was 3.1:2. The mean duration of follow-up was 15±4.7 years. The mode of transmission was mostly (60%) vertical (from mother to child), and 6% of the patients were vaccinated against hepatitis B. Although HBV immunoglobulin prophylaxis is used in Turkey to prevent the vertical transmission of CHB, the patients recruited in the present study were those whose mothers have not been prenatally screened for HBV; therefore, such patients have not been given HBV immunoglobulin prophylaxis.

Overall, 75% of the patients were HBeAg positive. All the 4 patients with concurrent HCV infection had been infected with HCV via blood transfusion. None of the patients had a family history of HCC. The clinical characteristics and laboratory results of the patients have been summarized in Table I.

Of the 270 patients, 12.2% (n=33) were HBV DNA negative and 87.8% (n=237) were positive at admission. HBV DNA levels could not be analyzed in 51 patients because the parents could not charge the cost of the tests. Of the 237 HBV DNA positive patients, 11% (n=26) were HBeAg negative, and these patients were regarded as mutant HBV infection (HBeAg-negative chronic hepatitis).

A mild correlation was observed between cirrhosis and HBsAg titer (r=0.298, p<0.006). A significant correlation was observed between HDV (n=4) and HCV (n=4) coinfections and cirrhosis (r=0.666, p<0.000 and r=0.213, p<0.000, respectively). No correlation was established among HBV DNA, HAI scores, and cirrhosis (r=0.130, p<0.112 and r=–0.046, p<0.447, respectively). Similarly, no correlation was observed between HBV DNA and cirrhosis (r=–0.046, p<0.447). The seroconversion rates between treat-

ed and untreated patients and their relationship with age; sex; vaccination status; mode of transmission; physical examination signs; initial laboratory results; and HBsAg, HBeAg, and HBV DNA titers are summarized in Table 2.

A total of 147 patients were treated with IFN alpha-2a (n=54), IFN alpha-2b (n=48), IFN alpha-2b and lamivudine (n=34), and IFN alpha-2a and lamivudine (n=11) during 6 months. The correlations among treatment modalities, and seroconversion rates are shown in Table 3.

TABLE I. Clinical characteristics of the patients at admission

Age (mean±SD, range years)	8.99±3.75 (0.75–17 years)
Sex (M/F)	197/124 (3.1:2)
Mode of transmission	
Mother	194 (60%)
Father	47 (14%)
Siblings	35 (11%)
Blood transfusion	32 (10%)
Surgical operation	7 (2%)
Other (tooth extraction, cousin vs)	6 (1.86%)
Hepatitis B vaccination	
Yes	302 (94%)
No	19 (6%)
HBeAg positivity	241 (75%)
Anti-HBe positivity	80 (25%)
Coinfection	
HDV	4 (1.24%)
HCV	4 (1.24%)
Splenomegaly	10 (3.1%)
Hepatomegaly	15 (4.6%)
Ascites	4 (1.2%)
Cirrhosis	5 (1.5%)
Biopsy	
Yes	147
No	174
HAI score	
Minimal	23 (16%)
Mild	68 (46%)
Moderate	35 (24%)
Severe	21 (14%)
Fibrosis stage	
None	13 (9%)
Minimal	91 (62%)
Mild	31 (21%)
Moderate	11 (7%)
Severe	1 (0.6%)

HBeAg: Hepatitis B e antigen; Anti-HBe: Hepatitis B e antibody; HDV: Hepatitis Delta virus; HCV: Hepatitis C virus

Only 97 of the 174 untreated patients were HBeAg positive. HBeAg seroconversion rates were 30/97 (30.9%) in untreated patients (spontaneous seroconversion) during 20.8±21.9 months and 67/147 (45.5%) in treated patients during 27.8±17.7 months (p=0.023) (Figure 1). HBsAg seroconversion rates were 10/174 (5.7%) in untreated patients (spontaneous seroconversion) during 13.9±12 months and 16/147 (10.8%) in treated patients during 26.5±11.9 months (p=0.10). No significant difference was observed in HBeAg and HBsAg seroconversion times between the two groups (p>0.05). No difference was also observed with respect to HBeAg and HBsAg seroconversion rates between treatment with IFN alpha-2a or IFN alpha-2b alone and in combined treatment with lamivudine (p=0.07 and p=0.64, respectively).

Although the HBeAg seroconversion rates were significantly higher in patients with high pretreatment HBV DNA and serum ALT levels (p=0.005), no significant difference was observed in HBsAg seroconversion rates in these patients. In addition, spontaneous seroconversion rates were not significantly different in patients with high serum ALT and HBV DNA levels (p>0.05).

HBeAg reversion was observed only in 3 of the 5 male patients [mean age 6±3.3 (range 3–11) years] with cirrhosis, whereas HBsAg seroconversion was observed in none of them. One of the two patients in whom seroconversion was not observed had concurrent HCV infection. None of these children with cirrhosis developed HCC. One of the patients with cirrhosis died of liver-related causes, and one of them underwent liver transplantation during follow-up.

DISCUSSION

The development of chronic HBV infection is higher in individuals infected perinatally (90%) or during childhood (20%–30%), which is thought to be due to immaturity of the immune system, than in adults (<1%) (1, 3). The most frequent mode of transmission is vertical transmission (from mother to child) in countries where moderate and high rates of HBsAg carriage are observed (1, 2). In our study, perinatally acquired HBV infection was observed in 60% of the patients. When compared with other transmission methods, no significant difference was observed in HBsAg and HBeAg seroconversion rates among patients who had vertical transmission of HBV.

Turkey is a moderate endemic area for HBV infection, and vaccination against hepatitis B is recommended for infants, children, and adolescents since 1998 in routine vaccination programs; therefore, 94% of our patients were unvaccinated against HBV.

Factors associated with an increased risk of developing liver diseases and progression to cirrhosis include older age (>40 years), male sex, presence of HBeAg, HBV genotype, mutations in the precore and core promoter regions of the viral genome, recurrent ALT flares, severity of fibrosis stage at presentation, HBV genotypes C>B and D>A, and concurrent infections (HBV/HCV and/or HBV/HDV) (1). In the present study, a correlation was established between cirrhosis and initial HBsAg titer, fibrosis score, and coinfections with HDV and HCV. Male sex has been identified as an independent risk factor of cirrhosis (8). Molecular mechanisms between sex and fibrosis are unknown, but the antifibrogenic effect of estrogen has been proposed (9).

TABLE 2. The association between seroconversion rates and clinical features and laboratory parameters

	HBeAg (+) patients (n=241)		HBeAg (–) patients (n=80)		
	Treated (n=141)	Untreated (n=100)	Treated (n=3)	Untreated (n=77)	P
Age (mean±SD)	8.2±3.9	8.9±4.1	5.5±4.27	10±3.8	0.81
Gender (M/F)	90/51 (1.7:1)	60/40 (1.5:1)	2/1 (2:1)	45/32 (1.4:1)	0.61
Vaccination status					
Yes	130 (92%)	94 (94%)	3 (100%)	75 (97.4%)	0.68
No	11 (7.8%)	6 (6%)	0	2 (2.5%)	0.34
Hepatomegaly	10	3	2	0	1.00
Splenomegaly	8	1	0	1	1.00
Ascites	3	0	1	0	1.00
Cirrhosis	5	0	0	0	1.00
Total bilirubin	0.8±0.76	0.7±0.61	0.9±0.62	0.8±0.35	0.91
AFP	591±504.9	540±470.2	536±450.3	520±460.1	1.00
Serum albumin	4.0±0.6	4.0±0.5	4.1±0.6	4.0±0.5	1.00
AST	104±158.6	72.7±144.7	38.6±16.2	113.9±269.2	0.82
ALT	114.6±152	89.2±121.1	54.3±23.1	126.8±306	0.56
HBV DNA	9455±12323	11224±14018	4589±2635	3973±8911	1.00
HAİ					
Minimal	22 (15.2%)	-	1 (33.3%)	-	1.00
Mild	68 (47.2%)	-	0	-	1.00
Moderate	34 (23.6%)	-	1 (33.3%)	-	1.00
Severe	20 (13.8%)	-	1 (33.3%)	-	1.00
Fibrosis stage					
None	12 (8.3%)	-	1 (33.3%)	-	1.00
Minimal	90 (62.5%)	-	1 (33.3%)	-	1.00
Mild	30 (20.8%)	-	1 (33.3%)	-	1.00
Moderate	11 (7.6%)	-	0	-	1.00
Severe	1 (0.69%)	-	0	-	1.00

AFP: alpha-fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HAI: hepatic activity index; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen
p<0.05 is statistically significant

In our patients with CHB and all patients with cirrhosis, 61.4% were male patients.

Longitudinal studies have demonstrated that HBeAg seroconversion leads to the inactive HBsAg carrier state in most children (1, 4, 10-12). Spontaneous HBeAg and HBsAg seroconversion rates occur at an average rate of approximately 10%–16% and 0.6%–1% per year, respectively (1, 4, 10-13). Spontaneous HBeAg seroconversion rates have also been reported to be <2% per year among children aged ≤3 years and 4%–5% per year in older children (>3 years) (13). In the present study, the spontaneous HBeAg seroconversion rate was 30.9% and spontaneous HBsAg seroconversion rate was 5.7%, and these seroconversion rates did not change according to age.

Long-term follow-up studies of adult inactive HBsAg carriers have shown that infection in these patients rarely progresses to cirrhosis or HCC (14). Patients who clear HBeAg with sustained reduction of HBV DNA, ALT normalization, and eventually HBsAg loss have a very low risk of developing HCC and have increased survival compared with patients with cirrhosis and persistent high levels of HBV replication. Cirrhosis is infrequent, its incidence is estimated to be 3%–4% in cohort studies (11, 15), and it has been reported to be an early complication. Among the 5 patients with cirrhosis, 3 were aged <4 years.

Hepatitis B virus DNA and ALT levels persistently or intermittently increase in some patients who undergo HBeAg seroconversion. These patients have a naturally occurring mutant form of HBV that abolishes or down-regulates the HBeAg promoter region (4) and are redetermined as having HBeAg-negative CHB. Progression to HBeAg-negative chronic hepatitis due to HBV variants not expressing HBeAg occurs at a rate of 1–3 per 100 person-years following HBeAg seroconversion (2). These patients have the ability to significantly replicate HBV

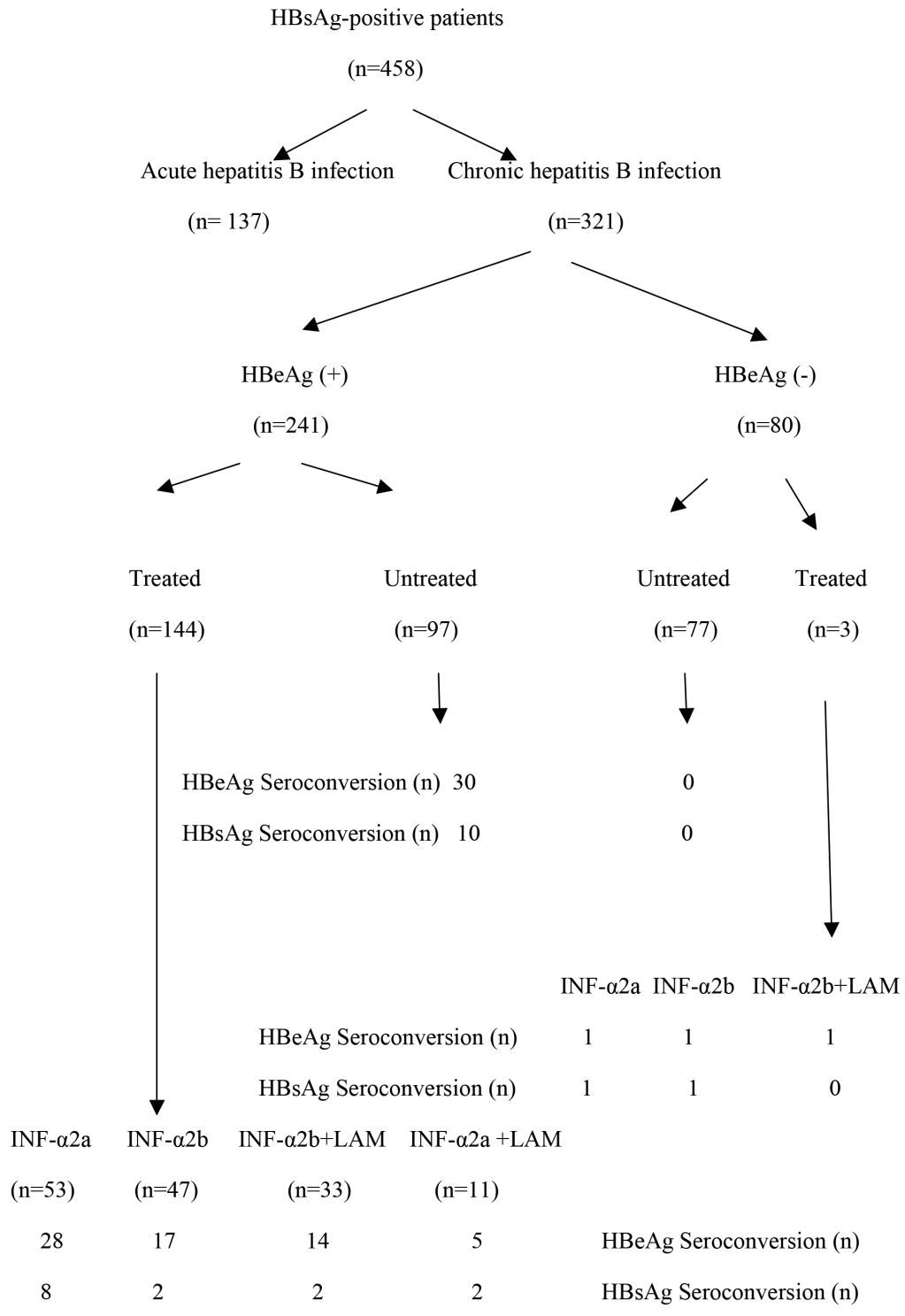

FIGURE I. Distribution of HBsAg-positive patients

in the presence of anti-HBe, even when ALT levels are normal. HBeAg-negative CHB is not typically acquired as a de novo infection, although there is reportof transmission of precore mutant HBV (16). Sustained spontaneous remission is uncommon in patients with HBeAg-negative CHB (6%–15%), and the long-term prognosis is poorer in HBeAg-negative patients than in HBeAg-positive patients (16). In our study, 32.5% of HBeAg-negative patients had HBV DNA positivity.

It has been reported that ALT is a poor predictor of outcomes and that IFN alone is not an appropriate indication for therapy (3, 17). The best predictors of adverse outcomes and treatment responses are HBV DNA levels in hepatitis B carriers (1, 17). ALT activity may be independently related to body mass index, sex, geographic origin, genotype, and abnormal lipid and carbohydrate metabolism, and ALT increases also occur during spontaneous HBeAg loss, in association with other viruses (18).

TABLE 3. The correlation between treatment modalities and seroconversion rates

Treated patients (n=147)	HBeAg seroconversion	HBsAg seroconversion	p
Interferon alfa-2a (n=54)	29 (53.7%)	9 (16.6%)	0.0001
Interferon alfa-2b (n=48)	18 (37.5%)	2 (4%)	0.0001
Interferon alfa 2b+lamivudine (n=34)	15 (44%)	3 (8.8%)	0.002
Interferon alfa-2a+lamivudine (n=11)	5 (45%)	2 (1.8%)	0.36
p<0.05 is statistically significant			

Keeffe et al. (18) reported that higher seroconversion rates are observed in patients who have high pretreatment serum ALT and HBV DNA levels than the patients who have normal serum ALT and HBV DNA levels. In our study, higher HBeAg seroconversion rates were also observed in patients with high pretreatment serum ALT and HBV DNA levels than in other patients, but spontaneous seroconversion rates were not different in these patients than other patients.

The primary aim of antiviral therapy is the elimination and durable suppression of serum HBV DNA to the lowest levels possible (maximally $<10^4$ and preferably $<10^3$) and prevention of the progression of liver diseases to cirrhosis (17). It has also been reported that, compared with no antiviral therapy, antivirals improve the HBV DNA suppression and frequency of ALT normalization and HBeAg seroconversion in children with CHB (18). IFN lacks resistance, is expensive, has to be administered via injections, and has many side effects such as flu-like symptoms, nausea, vomiting, anemia, autoimmune diseases, mood disorders, stroke and increased infections . Lamivudine is well tolerated, safe, and efficient, but it is also associated with high rates of resistance; therefore, it is not recommended as a first-line therapy in HBeAg-positive patients (19-23).

Fattovich et al. (15) and Iorio et al. (24) reported that antiviral treatment does not significantly influence HBeAg clearance, whereas Komatsu et al. (25) reported that antiviral treatment can accelerate the achievement of HBeAg seroconversion in children. HBeAg seroconversion rates have been reported to be 76%–86% in treated patients and 37%–75% in untreated patients (5, 19). Although some trials have suggested that combination therapy with IFN alpha-2a and lamivudine results in higher rates of HBeAg seroconversion, HBV DNA undetectability, and ALT normalization than those obtained by treatment with lamivudine alone (26-28), some trials have suggested no benefit and advantages of combination therapy over treatment with IFN alone with respect to HBeAg seroconversion in accordance with our study (29, 30).

HBeAg seroconversion rates have been reported to be 16%–40% with lamivudine treatment (31-32). Keeffe et al. (19) compared seroconversion rates according to the given treatment (IFN and lamivudine) and found that HBeAg seroconversion rates are 18% with INF and 16%–18% with lamivudine and that HBsAg seroconversion rate is 11%–25% with IFN. When compared, our seroconversion rates were higher at 46% with IFN alone and 44% with combined therapy with respect to HBeAg seroconversion. HBsAg seroconversion rates were similar at 10.7% with IFN alone and 11.1% with combined therapy. In our study, although the highest seroconversion rate was obtained with IFN alpha-2a treatment alone (n=29, 53.7%, p=0.0001), it is thought that it would not be used as a single agent in the treatment of CHB because of antiviral drug resistance. There was no difference in HBsAg seroconversion rates and seroconversion times between treated and untreated patients in our study.

It has been reported that the progression of liver diseases, perinatal transmission, and response to antiviral drugs may be influenced by genotypes (3). Keeffe et al. (19) recommended that patients should be routinely genotyped to help identify patients who may be at a greater risk for disease progression, particularly those who are the most appropriate candidates for treatment with IFN. The limitation of our study was that viral genotyping and sequence analysis were unavailable at our hospital.

In conclusion, a total of 30.9% patients underwent spontaneous HBeAg seroconversion and the spontaneous HBsAg seroconversion rate was 5.7%. No significant difference was observed between treated and untreated patients with respect to seroconversion rates and seroconversion times. Further well-designed prospective studies are needed to clarify the natural course of CHB and predictors of disease progression, such as HBV genotypes, mutants, and viral load, for improving the management of children with CHB.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - N.U.; Design - N.U., D.K.; Supervision - N.U.;Resource - N.U.; Materials - N.U., D.K.; Data Collection and/or Processing - N.U., D.K.; Analysis and/or Interpretation - N.U., D.K.; Literature Search - D.K.; Writing - D.K., N.U.; Critical Reviews - N.U.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: Special emphasis on disease progression and prognostic factors. J Hepatol 2008; 48: 335-52. [CrossRef]
2. de Francis R, Hadengue A, Lau G, Lavanchy D, Lok A, McIntyre N, et al. EASL International Consensus Conference on Hepatitis B 2002 Geneva,Switzerland Consensus statement. J Hepatol 2003; 39: P3-25. [CrossRef]
3. Jonas MM, Block JM, Haber BA. Treatment of children with chronic hepatitis B virus infection in the United States: Patient selection and therapeutic options. Hepatology 2010; 52: 2192-205. [CrossRef]

4. Mendy ME, McConkey SJ, Sande van der MAB, Crozier S, Kaye S, Jeffries , et al. Changes in viral load and HBsAg and HBeAg status with age in HBV chronic carriers in The Gambia. Virol J 2008; 5: 1-8. [CrossRef]
5. Marx G, Martin SR, Chicoine JF, Alvarez F. Long-term follow-up of chronic hepatitis B virus infection in children of different ethnic origins. J Infect Dis 2002; 186: 295-301. [CrossRef]
6. Jonas MM. Hepatitis B virüs infection in children. Clin Liver Dis (Hoboken) 2013; 2: 41-4. [CrossRef]
7. Knodell RG, Ishak KG, Black WC,Chen TS, Craig R, Kaplowitz N, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981; 1: 431-5. [CrossRef]
8. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-In HBV (the REVEAL-HBV) Study Group. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load Gastroenterology 2006; 130: 678-86. [CrossRef]
9. Shimizu I. Impact of oestrogens on the progression of liver disease. Liver Int 2003; 23: 63-9. [CrossRef]
10. Ni YH, Chang MH, Chen PJ, Tsai KS, Hsu HY, Chen HL, et al. Viremia profiles in children with chronic hepatitis B virus infection and spontaneous e antigen seroconversion. Gastroenterology 2007; 132: 2340-5. [CrossRef]
11. Bortolotti F, Guido M, Bartolacci S, Cadrobbi P, Crivellaro C, Noventa F, et al. Chronic hepatitis B in children after e antigen seroclearance: Final report of a 29-year longitudinal study. J Hepatol 2006; 43: 556-62. [CrossRef]
12. D'Antiga L, Aw M, Atkins M, Moorat A, Vergani D, Mieli-Vergani G. Combined lamivudine/interferon-alpha treatment in "immunotolerant" children perinatally infected with hepatitis B: a pilot study. J Pediatr 2006; 148: 228-33. [CrossRef]
13. Mieli-Vergani G, Vergani D. Treatment of hepatitis B virus in children. Why, whom, how? Indian J Gastroenterol 2006; 25: 121-4.
14. Chang MH. Hepatitis B virus infection. Semin Fetal Neonatal Med 2007; 12: 160-7. [CrossRef]
15. Fattovich G. Natural history and prognosis of hepatitis B. Semin Liver Dis 2003; 23: 47-58. [CrossRef]
16. Hadziyannis SJ. Hepatitis B e antigen negative C hepatitis B: from clinical recognition to pathogenesis and treatment. Viral Hep Rev 1995; 1: 7-36.
17. Sherman M. Predicting survival in hepatitis B. Gut 2005; 54: 1521-3. [CrossRef]
18. Jonas MM, Lok ASF, McMahon BJ, Brown RS, Wong JB, Ahmed AT, et al. Antiviral therapy in management of chronic hepatitis B viral infection in children: A systematic review and meta-analysis. Hepatology 2016; 63: 307-18. [CrossRef]
19. Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. Clin Gastroenterol Hepatol 2006; 4: 1-27. [CrossRef]
20. Sokal EM, Paganelli M, Wirth S, Socha P, Vajro P, Lacaille F, et al. Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines: consensus of an expert panel on behalf of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Hepatol 2013; 59: 814-29. [CrossRef]
21. Della Corte C, Nobili V, Comparcola D, Cainelli F, Vento S. Management of chronic hepatitis B in children: an unresolved issue. J Gastroenterol Hepatol 2014; 29: 912-9. [CrossRef]
22. Shah U, Kelly D, Chang MH, Fujisawa T, Heller S, González-Peralta RP, et al. Management of chronic hepatitis B in children.J Pediatr Gastroenterol Nutr 2009; 48: 399-404. [CrossRef]
23. Komatsu H, Inui A, Fujisawa T. Pediatric hepatitis B treatment. Ann Transl Med 2017; 5: 37. [CrossRef]
24. Iorio R, Tufano M, Giagnorio MG, Spagnuolo MI, Giannattasio A. What evidence exists to support antiviral treatment in children with chronic hepatitis B? Antivir Ther 2014; 19: 225-7. [CrossRef]
25. Komatsu H, Inui A, Sogo T, Tsunoda T, Fujisawa T. Chronic hepatitis B virus infection in children and adolescents in Japan. J Pediatr Gastroenterol Nutr 2015; 60: 99-104. [CrossRef]
26. Popalis C, Yeung LTF, Ling SC, Ng V, Roberts EA. Chronic hepatitis B virus (HBV) infection in children:25 years experience. J Viral Hepat 2013; 20: 20-6. [CrossRef]
27. Selimoglu MA, Ertekin V, Karabiber H. Treatment results of chronic hepatitis B in children: a retrospective study. Turk J Pediatr 2010; 52: 360-6.
28. Barbaro G, Zechini F, Pellicelli AM, Francavilla R, Scotto G, Bacca D, et al. Long-term efficacy of interferon alpha-2b and lamivudine in combination compared to lamivudine monotherapy in patients with chronic hepatitis B: an Italian multicenter randomized trial (abstr). Hepatology 2001; 34: 318A. [CrossRef]
29. Schalm S, Heathcote J, Cianciara J, Farrell G, Sherman M, Willems B, et al. Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection:a randomised trial. Gut 2000; 46: 562-8. [CrossRef]
30. Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005; 352: 2682-95. [CrossRef]
31. Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004; 351: 1206-17. [CrossRef]
32. Jonas MM, Kelly D, Mizerski J, Badia I, Areias J, Schwarz K, et al. Clinical trial of lamivudine in children with chronic hepatitis B. N Engl J Med 2002; 346: 1706-13. [CrossRef]