Research Article

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The Effect of Switch Treatment on Liver Fibrosis and qHBsAg Levels in Patients with Chronic Hepatitis B

Kronik Hepatit B Hastalarında Switch Tedavisinin Karaciğer Fibrozu ve qHBsAg Düzeylerine Etkisi

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ABSTRACT

Objectives: The aim of this study was to evaluate the relationship between clinical, biochemical, serological parameters, fibroscan imaging in terms of fibrosis and quantitative hepatitis B surface antigen (qHBsAg) levels in patients with chronic hepatitis B (CHB) infection whose treatment has been switched from LAM to TDF.

Materials and Methods: The study included 19 patients with CHB and under the LAM treatment. The gender, age, comorbidity, medications, routine laboratuary, creatinine clearance, bone mineral density, transient elastography for stage of liver fibrosis and qHBsAg level were examined.

Results: Ten of 19 patients were female and 9 were male. When the qHBsAg titers of the patients at 6th and 12th months were compared, there was a statistically significant decrease in qHBsAg titers of the patients after the 12th month. There was a significant decrease in liver fibrosis measurements at the 12th month of treatment change. There was a statistically significant positive correlation between qHBsAg titers and fibroscan values at baseline and 12th month.

ÖZ

Amaç: Bu çalışmanın amacı, tedavisi LAM'den TDF'ye geçen kronik hepatiti B (KHB) enfeksiyonu olan hastalarda klinik, biyokimyasal, serolojik parametreler, fibroskan görüntüleme ile fibrozis ve kantitatif hepatit B yüzey antijeni (qHBsAg) düzeyleri arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya LAM tedavisi altındak 19 KHB hastası dahil edildi. Cinsiyet, yaş, yandaş hastalıkları, ilaçlar, rutin laboratuvar tetkikleri, kreatinin klirensi, kemik mineral dansitesi, fibrozis derecelendirmesi için transient elastografi ölçümü ve qHBsAg seviyeleri belirlendi.

Bulgular: 19 hastanın 10'u kadın 9'u erkekti. Hastaların 6. ve 12. ayındaki qHbsaq titreleri değerlendirildiğinde, 12. ayın sonunda qHBsAg titrelerin anlamlı ölçüde düşüş saptandı.

Karaciğer fibrozis ölçümlerinde de tedavi değişikliğinin 12. ayında anlamlı düşüş saptandı. Başlangıçtaki ve 12. aydaki qHBsAg titreleri ile fibroscan ölçümleri arasında istatistiki olarak anlamlı bir pozitif korelasyon saptandı.

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Conclusion: In this study, the replacement of LAM with TDF may prevent the resistance problem, and also the decrease in fibrosis values and/or qHBsAg levels may contribute to the prevention of HCC and cirrhosis have been showed.
Keywords: Lamivudine, tenofovir, switch treatment, liver fibrosis, hepatitis B

Sonuç: Bu çalışmada LAM yerine TDF'ye geçilmesi ile direnç probleminin çözülebileceği, aynı zamanda qHBsAg titrelerinde ve fibrozis değerlerinde düşüş sağlanarak HCC ve sirozdan da korunulabileceği gösterilmeye çalışılmıştır.
Anahtar Kelimeler: Lamivudin, tenofovir, tedavi değişikliği, karaciğer fibrozis, hepatit B

Introduction

Chronic hepatitis B (CHB) virus infection is the most common cause of cirrhosis, end stage liver disease, hepatocellular carcinoma (HCC) and death from liver disease in Turkey. Since long term suppression of HBV replication with antivirals is associated with histological improvement, the main goal of therapy for (CHB) is to suppress HBV replication in a sustained fashion and thereby to prevent progression to cirrhosis and development of HCC. Currently, there are 2 classes of drugs approved for the treatment of CHB: pegylated interferon alfa and nucleot(s)ide analogues, i.e. lamivudine, adefovir, entecavir, tenofovir and telbivudine.

Lamivudine is the first nucleoside analogue for the treatment of CHB. Lamivudine has been shown to be effective in patients with hepatitis B e antigen [HBeAg (+)] and HBeAg (-) chronic HBV infection whether they had compensated and decompensated cirrhosis (1,2). In treatment naive patients with HBeAg (+) CHB, HBeAg seroconversion rates were shown to be 16-18% at year 1 (3).

In HBeAg (-) CHB, undetectable HBV-DNA levels were achieved in 60-70% of patients at year 1; however, HBV DNA became positive in 90% of patients after stopping therapy (4,5). Lamivudine was also shown to prevent disease progression, HCC development, and the need for liver transplantation in compensated and decompensated cirrhosis (6,7,8). However, resistance to lamivudine develops in 11-24% of patients with HBeAg (+) CHB and 6-18% of those with HBeAg (-) CHB, and reaches up to 70% of patients after 8-year treatment (9).

Tenofovir is a potent nucleotide analogue with high genetic barrier to resistance (10). It is effective in both treatment naive and lamivudine/entecavir resistant chronic HBV infection (11). In HBeAg (+) CHB, tenofovir achieved undetectable HBV-DNA levels in 76%, HbeAg seroconversion in 21%, hepatitis B surface antigen (HbsAg) seroconversion in 3%, alanine aminotransferase (ALT) normalization in 68% and histological improvement in 74% of patients after 1-year therapy. In HBeAg (-) CHB, tenofovir achieved undetectable HBV-DNA levels in 93%, ALT normalization in 76% and histological improvement in 72% of patients after 1-year therapy (12). According to recently published EASL and AASLD guidelines, tenofovir is one of the first-line therapies for CHB (1,13).

In the present study, we aimed to evaluate the efficacy of tenofovir in chronic hepatitis B patients in whom serum HBV-DNA had become negative on lamivudine therapy and it was switched to tenofovir in the absence of lamivudine resistance with respect to biochemical and serological responses. We also aimed to evaluate the efficacy of tenofovir on liver fibrosis by transient elastography and associations of these variables with quantitative HBsAg (qHBsAg) levels.

Materials and Methods

The study included 19 CHB patients who had been followed up at gastroenterology outpatient clinic. Patients were screened for serum HBV-DNA, [aspartate aminotransferase (AST), ALT, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT)], albumin, bilurubin, prothrombin time and creatinin levels. Of them, patients who were on lamivudine therapy and had undetectable serum HBV-DNA were included. 3 cc blood samples were obtained from patients for the measurement of serum qHBsAg.

After centrifuged, serum samples were stored in deep freeze at -80 °C. At 6th and 12th months of therapy, same procedures were repeated. At the end of study period, serum qHBsAg levels were measured using Abbott Architect i2000sr device and Abbott ArchitectHBsAg 6C36 quantitative kit which was based on chemiluminescent microparticle immonoassay. Serum qHBsAg concentration ≥0.05 IU/mL was considered positive. When qHBsAg was > 250.00 IU/mL, serum samples were 1/500 diluted.

Anti-HBc, anti-HBs, HBeAg, and anti-HBe were measured using AbbottArchitect i2000sr device. Serum HBV-DNA was measured using Rotor-Gene Q, Qiagen device and Artus HBV QS-RGQ kit by real time polymerase chain reaction (PCR).

Serum and urine biochemistry tests were measured using Abbott/Architect C16000 device. Twenty four-hour urinary protein was measured by turbidimetric assay using benzethonium chloride as denaturating agent. Liver fibrosis was evaluated by transient elastography using CAP featured Fibroscan 502 Touch (SNF60121)-Probe xl (SN90226)-c2.0.0.0 at the start and 12th month of TDF therapy.

The liver stiffness measurement results were expressed in 1.5-75 kPa and CAP measurement results were expressed in 100-400 dB/m. Liver stiffness measurement was performed by one physician and factors that might hamper the liver stiffness were taken into account. More than 10 successful acquisitions, success rate >60% and IQR/M rate <30% were considered reliable.

Lamivudin was switched to TDF 245 mg qd. Written informed concent was obtained form the all patients. Local Ethic Committee approval was taken from the Kocaeli University with the approval number of 21.91016-2016/15.2.

Statistical Analysis

Statistical analyses were made using SPSS (SPSS, Inc, Chicago, IL, USA) for Windows 17.0. For the evaluation of the study data, in addition to descriptive statistical methods (mean ± standard deviation), the Student's t-test and the Mann-Whitney U test were used to establish potential differences between the averages of two independent groups for parameters with and without normal

distributions, respectively. One-Way ANOVA test and Friedman test were used for the comparison of dependent quantitative variables. Correlation analysis between quantitative variables were performed using Pearson correlation test. For comparisons of qualitative data, the chi-squared test was used. The results in the 95% confidence interval and p values <0.05 were considered to be significant.

Results

The study included 19 patients. All patients were Caucasian, and 10 of them were (52.6%) were female with a mean age of 54.7±9.6 years. Eight patients (42.1%) were smoker and none of them were alcohol drinker. Body mass index was 25.0-29.9 kg/m^2 in 9 patients (47.4%), 30.0-39.9 kg/m^2 in 2 patients (9.5%), and ≥40.0 kg/m^2 in 3 patients (6.3%). None of them had family history of hepatocellular carcinoma. HBeAg was negative in all patients.

Liver stiffness measurements at the beginning and 12th month of therapy were 7.4±3.8 kPa and 6.2±2.9 kPa, respectively (p=0.013). Decreasing in liver stiffness measurement was 0.95 (0.30-2.37) kPa. Liver stiffness measurement was decreased in 17 patients (89.4%) and increased in 2 patients (10.6%).

At the beginning of therapy, 11 patients had osteopenia (57.9%) and 8 patients had normal bone mineral density (43.1%). At the 12th month of therapy, 12 patients had osteopenia (47.4%) and 10 patients had normal bone mineral density (52.6%). The difference in bone mineral density between the beginning and the 12th month of therapy was not statistically significant (p=0.500).

There was not statistically significant difference in qHBsAg levels between the beginning and the 6th month of therapy (p=0.114). However, qHBsAg levels showed a significantly (p=0.003) decreasing as 9.1±18.5% at the 12th month of therapy while comparing with the beginning.

There was statistically significant correlation between decrease in qHBsAg levels and improvement in liver stiffness measurement (Table 1).

Discussion

Lamivudin has been used in the treatment of chronic HBV infection; however, resistance is an important problem due to low genetic barrier. Although it effectively suppress HBV replication in the short term, virological breaktrough and flare can occur due to mutations.

Therefore, lamivudin is no longer recommended as a first line therapy in the treatment of chronic HBV infection (14,15,16).

The frequency of resistance to oral antivirals increases as the time goes by. After 5 years of therapy, resistance to lamivudin and adefovir reaches to 70% and 29%, respectively.

Table 1. Correlation between qHBsAg and liver stiffness measurement

		Fibroscan 1	Fibroscan 2
HBsAg 0	r	0.511	0.502
	p	0.030	0.028
HBsAg 12	r	0.492	0.476
	p	0.038	0.039

HbsAg: Hepatitis B surface antigen

Resistance to telbivudin was reported as 22% after 2 years. On the other hand, resistance to entecavir is only about 1.2% and resistance to tenofovir has not been reported yet (13,17).

Besides effective and maintained suppression HBV replication, another goal of therapy is prevention of side effects. Because of low antiviral activity and low genetic barrier to resistance, lamivudin is no longer recommended as a first line therapy in the treatment of chronic HBV infection (18).

In a study by Marcellin et al. (19) 5-year TDF therapy resulted in histologic improvement in 87% patients and regression of fibrosis in 51% of patients. Only 9 of 641 patients developed side effect which had led to discontinuation of therapy (19). In the present study, histological improvement rate ocurred in 17 of 19 (89.7%) of patients.

Routine follow up with liver biopsy is not recommended to monitör histological improvement due to its invasiveness and complications. Moreover, repeat liver biopsy result does not lead to therapy modification. Therefore, noninvasive tests are used to evaluate the efficacy of antivirals on histological activity. Of them, fibroscan is increasingly used to evaluate liver fibrosis.

In meta-analysis of 50 studies, the area under the receiver operating characteristic (ROC) curves of fibroscan to predict significant fibrosis (F2), advanced fibrosis (F3) and cirrhosis (F4) were 0,84 (95% CI, 0.82-0.86), 0.89 (95% CI, 0.88-0.91) and 0.94 (95% CI, 0.93-0.95), respectively. As a result, transient elastography seems excellent in the prediction of cirrhosis and successfull in the prediction of advanced fibrosis, while there is variation in the prediction of significant fibrosis according to etiology of liver disease (20).

In an Asian metaanalysis, the area under the ROC curves of fibroscan to predict significant fibrosis (F2), advanced fibrosis (F3) and cirrhosis (F4) in chronic hepatitis B patients were 0.859 (95% CI, 0.857-0.860), 0.887 (95% CI, 0.886-0.887) and 0.929 (95% CI, 0.928-0.929), respectively (21). In another metaanalysis, Tsochatzis et al. (22) evaluated the diagnostic value of transient elastopgraphy. In this study, threshold liver stiffness measurement for F2, F3 and F4 fibrosis were 7, 9.5 and 12 kPa, respectively. Transient elastography had good sensitivity [0,83 (95% CI 0.79-0.86)] and specifity [0.89 (95% CI 0.87-0.91)] in the prediction of cirrhosis; however, they concluded that it should be used with caution in thew prediction different fibrosis stages in daily practice because there was not approved threshold values (22). In a cross sectionel study, the thresholds in the prediction of F2, F3 and F4 fibrosis were 6,9, 7,9 and 9,6 kPa, respectively (23). In the present study, liver fibrosis was improved significantly after 1 year therapy with TDF. Although the duration of treatment was short, the improvement in liver fibrosis is important and seems a valuable clue in the choise of antiviral agent.

HBsAg quantification has not been established in treatment monitorization yet. It was shown that there was correlation between cccDNA and intrahepatic HBV-DNA, and qHBsAg (24). In the present study, serum HBV DNA levels remained undetectable throughout therapy.

Moreover, qHBsAg levels decreased significantly after 1 year of TDF therapy. In a study, Pfefferkorn et al showed that qHBsAg level was reliable marker to establish inactive HBV carrier state (25). Tan et al. (26) showed that qHBsAg was not a reliable marker to

differentiate HBeAg negative chronic hepatitis B and inactive HBV carrier state. Sali et al. (27) also found similar results. On the other hand, there are studies who showed opposite findings (28,29). In the present study, decrease in qHBsAg levels supports TDF has favorable effects on cccDNA and intrahepatic HBV despite small number of patients.

Study Limitations

The most important limitations of our study are the small number of patients and the patients were evaluated without biopsy.

Conclusion

Potents antivirals as TDF should take place of lamivudin in the treatment of chronic hepatitis B. Significant decreasing in liver stiffness measurement and qHBsAg levels at long term can prevent the development of cirrhosis and hepatocellular carcinoma. There is need for studies made with large patient groups and in long term following up.

Ethics

Ethics Committee Approval: Local Ethic Committee approval was taken from the Kocaeli University Faculty of Medicine (approval number: 21.91016-2016/15.2).

Informed Consent: Verbal and written informed consent received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Y., F.G., Concept: M.S., G.Ş., Design: M.S., G.Ş., Data Collection or Processing: S.B.A., G.D., Analysis and/or Interpretation: S.B.A., M.K., Literature Search: E.Y., H.S., Writing: E.Y., M.K.

Conflict of Interest: All authors declare to have no conflict of interest.

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