Klinik Araştırma

Beta-2 Microglobulin as A Prognostic Factor in Chronic Hepatitis B Treatment

Kronik Hepatit B Tedavisinde Prognostik Faktör Olarak Beta-2 Mikroglobulin

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ÖZET

Amaç: *Kronik Hepatit B(KHB) hastalarında Beta-2 mikroglobulin (β-2 MG) seviyesi, inaktif taşıyıcılarına göre yüksek gözlemlenmiştir. β-2 MG seviyesi KHB'larında interferon tedavisi ile arttığı izlenmiştir. Bu çalışmanın amacı interferon tedavisi alan hastalarda tedavi öncesi ve sonrası β-2 MG seviyeleri arasındaki ilişkiyi araştırmaktır.*

Gereç ve Yöntem: *Bu Çalışma Kırıkkale Üniversitesi Tıp Fakültesi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji bölümü tarafından yürütüldü. Çalışmada hastalar iki gruba ayrıldı. Grup 1 daha önce tedavi almış veya ilk kez tedavi alan hastalardan oluştu(Bu hastalar HBsAg (+), HBV DNA (+), knodell skoru 4<, KCFT normal veya yüksek olan hastalar). Grup 2 kontrol grubu olarak belirlendi. Bu hastalar inaktif hepatit B taşıyıcısı olan hastalardan oluşuyordu(HBsAg (+), HBV DNA(-), KCFT normal) β-2 MG seviyeleri (AIDA autoimmune diagnostic assays, Ref 10801) cihazı ile microELİSA metodu kullanılarak değerlendirildi. Grup 1 hastalarında hem tedavi öncesi hem de tedaviden 2 ay sonra β-2 MG testi yapıldı.*

Bulgular: *Grup 1'deki hastaların yaşları 17-59 arasında idi(Ortalama:38). Grup2'de ise yaşlar 21-57 arasında iken ortalama yaş 44'idi. Her iki grup arasında ortalama yaş ve cinsiyet açısından anlamlı bir fark yoktu.(p=0.177, p=0.181, sırasıyla). Grup 1 hasta grubunda β-2 MG seviyeleri kontrol grubuna yüksek saptandı(p=0.0001). Ayrıca Grup 1 hasta grubunda tedavinin ikinci ayında β-2 MG sevileri anlamlı bir şekilde düşük saptandı.*

Sonuç: *β-2 MG değerleri Kronik hepatit B tedavisine başlamada ve tedavinin başarısını takipte bir parametre olabileceği düşünüldü. Bu konuda geniş kapsamlı çalışmalara ihtiyaç bulunmaktadır.*

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ABSTRACT

Aim: *The β-2 MG (Beta-2 microglobulin) levels in patients with chronic hepatitis B are observed to be significantly higher compared to the inactive carriers. In chronic hepatitis B infections treated with interferon, the β-2 MG levels have been observed to be higher during exacerbations. The aim of this study is to investigate the relationship between the β-2 MG levels before and after treatment in patients who are treated with interferon.*

Material and method: *The present study was conducted at the Kirikkale University Medical School, Department of Infectious Diseases and Clinical Microbiology. The study subjects were divided into two groups: Group 1 consisted of 22 patients who were both pre-treated for hepatitis B or were treatment-naive. They were also HBsAg (+) and HBV DNA (+). Their Knodell score was 4 or above in the liver biopsy and the liver enzymes were at least twice as high as the normal values. Group 2 was the control group and consisted of 22 inactive carriers who were HBsAg (+) and HBV DNA (-) with normal liver enzymes. The patients' β-2 MG levels (AIDA autoimmune diagnostic assays, Ref 10801) were analysed with the microELISA method using the serums that were stored at -70°C. The β-2 MG tests of the patients in Group 1 were essayed both before the treatment and 2 months into the treatment.*

Results: *The ages of the patients in the case of group varied between 17 and 59 (mean age: 38), while the age of the control group were between 21 and 57 (mean age: 44). No statistically significant difference has been observed in terms of the age and sex of the treatment and the control groups (p=0.177, p=0.181, respectively). There was a statistically significant difference between the starting β-2 MG values of case of group and the starting β-2 MG values of control group (p=0.0001). The β-2 MG levels in Group 1 were observed to be significantly lower in the 2nd month of the treatment.*

Conclusion: *The β-2 MG values have been thought to be auxiliary parameters both in the follow up of the treatment success and to make the decision to initiate the treatment. More comprehensive studies are required to clarify this issue.*

INTRODUCTION

In chronic hepatitis B infection, the main purpose of the treatment is the reduction of the serum HBV DNA levels, normalisation of the ALT, improvement of the liver histopathology and cessation of the fibrogenesis in the liver (1). The criteria for the complete response in chronic hepatitis B treatment are the loss of the HBsAg in the serum and negative readings of PCR and HBV DNA. Partial response is defined by the loss of HBV DNA and HBeAg from the serum (2). The rate of seroconversion (loss of HBeAg and production of anti-HBe) brought about by the interferon, which is one of the treatment modalities in chronic hepatitis B, is reported to be highly variable according to the studies and has always been observed to be higher (5-7%) than untreated patients (3). When the numerous side effects and high treatment costs are taken into consideration, the parameters used to assess the success of interferon treatment in chronic hepatitis B gain in importance. The β-2 MG (Beta-2 microglobulin) levels are significantly higher in patients with chronic hepatitis B infection compared to inactive carriers and they play a key role in the response to viral infections. The β-2 MG, which is an integral part of the human leukocyte antigen class 1 (HLA–1), is a protein with low molecular weight present in all cells with a nucleus. HLA–1 is found on the surfaces of the T- and B-lymphocytes besides various organs (4). In chronic hepatitis B infections treated with interferon, the levels of β-2 MG have been observed to be higher during exacerbations or in times when no treatment response could be achieved. In a study conducted on β-2 MG levels, a relationship has been observed with the virological breakthrough that occurs in the patients who take antiviral treatment. Thus, the β-2 MG has been suggested as a predictive marker for the virological breakthrough (4). The aim of this study is to investigate the relationship between the β-2 MG levels and the treatment response in patients receiving interferon treatment.

MATERIAL AND METHOD

Enrollment criteria: Group 1 (Case of group): Patients who had presented to the Department of Infectious Diseases and Clinical Microbiology, and were both pre-treated for hepatitis B or were treatment-naive were enrolled in this study. They were also HBsAg (+) and HBV DNA (+). The patients had a Knodell score of 4 or above in the liver biopsy and their liver enzymes were at least twice as high as the normal values. This patient group received pegylated interferon treatment.

Group 2 (Control group): Twenty-two inactive carriers who were HBsAg (+), HBV DNA (-) and had normal liver enzymes formed the control group. This group was untreated The age and sex of all the individuals enrolled in the study were recorded. Before the treatment, the sera of the treatment and control groups were collected and stored at a temperature of -70˚C. Also at the beginning of the study, the patients' HBV DNA levels were quantified. All the patients in the treatment group underwent a blood test for ANA, anti-DNA, free T3, free T4, TSH, hemogram (white blood cells, haemoglobin, hematocrit, platelet count), sedimentation, CRP, and biochemistry (urea, creatinine, ALT, AST, ALP, GGT, total bilirubin, direct bilirubin). The sera stored at -70 ºC were essayed for β-2 MG with the microELISA method (AIDA autoimmune diagnostic assays, Ref 10801). When we look at the treatment response criteria, in patients treated with peginterferon, HBV DNA levels <2.000 IU/ml at the 24th week indicated the virologic response; seroconversion in HBeAg positive patients indicated the serologic response; normalized ALT levels indicated the biochemical response; and loss of HBsAg together with the serologic and biochemical response indicated a complete response. The Beta-2 microglobulin levels have been tested both in the treatment group and the control group. In the treatment group, the Beta-2 microglobulin levels were also tested in the second month of the therapy. While virologic response was observed in 10 patients in the sixth month of the treatment, two patients dropped out of therapy in the sixth month due to intolerance. HbeAg seroconversion was observed in three patients.

Statistical analyses: The obtained data were analysed with the SPSS 8.0 statistical software and the statistical analyses included the Mann-Whitney U-test, Wilcoxon Signed Ranks Test, and Spearman's correlation analysis.

RESULTS

For the purposes of this study, 22 patients who had presented to the Department of Infectious Diseases and Clinical Microbiology and were diagnosed with chronic hepatitis B (case of group) were enrolled.

Twenty-two inactive HBsAg carriers were also enrolled as the control group (control group). The ages of the treatment group varied between 17 and 59 (mean age: 38), while the age of the control subjects were between 21 and 57 (mean age: 44). No statistically significant difference has been observed in terms of the age and sex of the treatment and control groups (p= 0.177, p=0.181, respectively). The duration of the disease in the treatment group was between 2 and 120 months (mean duration: 36 months). No significant difference has been observed between the duration of the disease and the success of the treatment (p=0,891). There was a statistically significant difference between the starting β-2 MG valu-es of Group 1 and Group 2 (p=0.0001) and the starting β-2 MG values were observed to be higher in the treatment group. The readings are shown in Figure 1. Also, while the mean value of the beta-2 microglobulin was 3.14 before the initiation of the treatment in the treatment group, this value was found as 2.84 during the second month of the treatment. This difference was statistically significant (P<0.001). The correlation analysis that included the β-2 MG and ALT levels of the treatment and control groups did not point out any statistically significant relationship.

DISCUSSION

Chronic hepatitis B infection is a very serious health problem since it may lead to liver cirrhosis and hepatic cancer. Reduction of the serum HBV DNA levels, normalisation of the ALT, improvement of the liver histopathology and cessation of the fibrogenesis in the liver are the main purposes of the treatment (1). Therefore, the HBsAg, HBeAg, HBV DNA, and ALT levels are used as the control parameters in chronic hepatitis B treatment. The criteria for the complete response in chronic hepatitis B treatment are the loss of the HBsAg in the serum, and negative readings of PCR and HBV DNA. Partial response is defined by the loss of the HBV DNA and HBeAg from the serum (2). When the numerous side effects and the high treatment costs are taken into consideration, the parameters used to assess the success of interferon treatment gain in importance. For this reason, the ALT, AST, HBV DNA levels, hyaluronic acid, uronic acid, type 4 collagen, type 3 procollagen, N-peptide (PIIIP), matrix metalloproteinase (MMP–1), laminine -which is the tissue inhibitor of matrix metalloproteinase-1 (TIMP–1)- and β-2 MG levels have been investigated as early indicators of the early

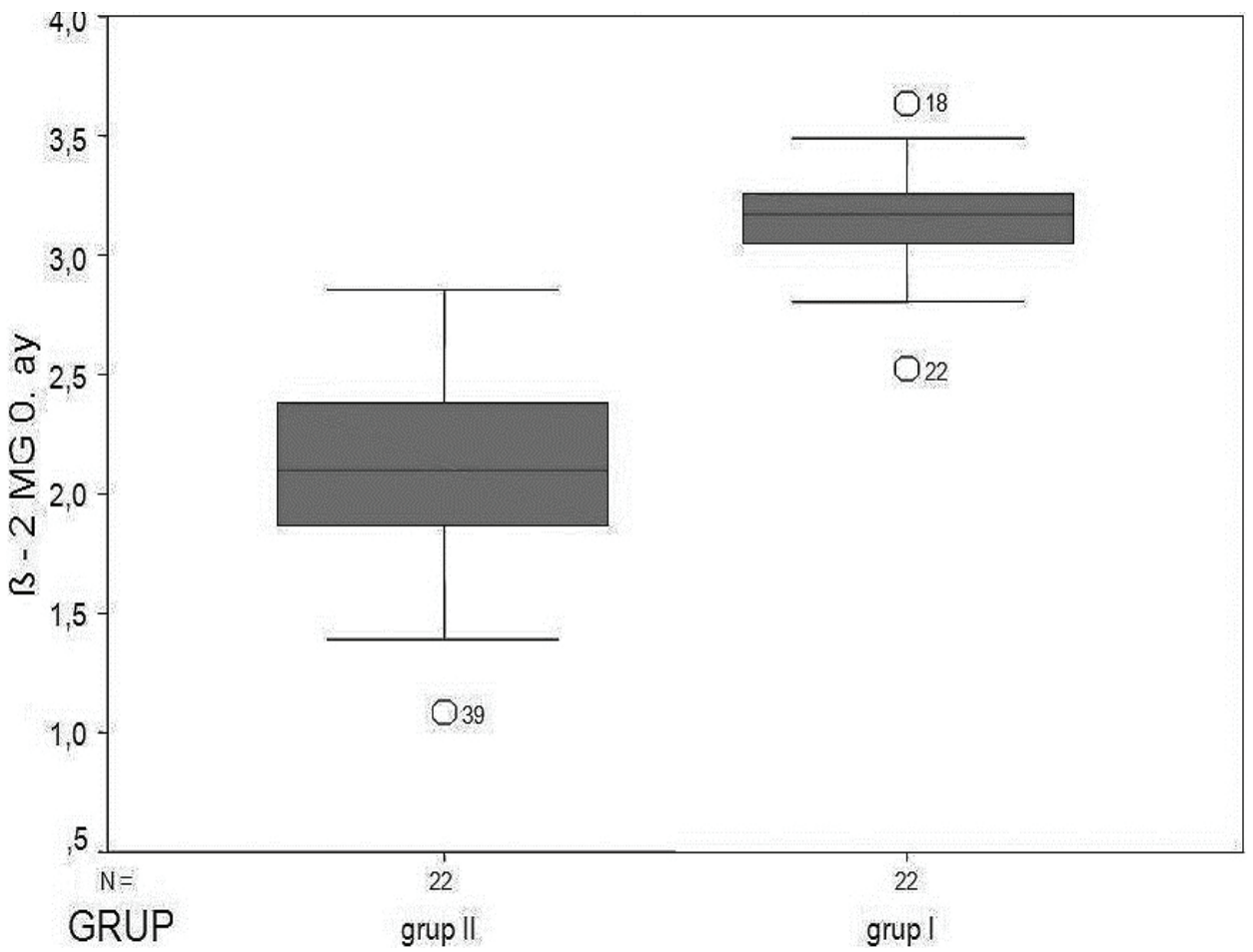

Figure 1. Both groups starting ß-2MG levels.

treatment response. Studies have shown that hyaluronic acid, type 3 collagen, PIIIP, MMP–1, TIMP-1 and laminine levels are associated with fibrosis (5). In the study by Malaguernera et al., where they investigated the relationship between the β-2 MG levels and the histological activity index in chronic hepatitis C patients, a significant correlation was demonstrated between the histological activity index and the β-2 MG levels (6). In another study conducted in patients with hepatocellular cancer related to the HCV, a similar significant relationship was observed between the β-2 MG levels and the tumour markers and sizes. Thus, the weakening in the immune system was thought to lead to the progression of the hepatocellular cancer and the hyperexpression of the β-2 MG (7). Another study on chronic hepatitis C patients treated with interferon alpha, where the effect of the treatment on the CD4 lymphocyte ratios and the β-2 MG levels in the peripheral blood were investigated, the interferon treatment was observed to lead to an increase in the β-2 MG levels (8). The same study revealed that the greatest increase in the β-2 MG levels was observed in the patients in whom the virus could not be removed from the serum. Therefore, increasing β-2 MG levels at the beginning of the treatment could be a predictive factor for a diminished success of the treatment, whereas increasing CD4 levels at the beginning may point to a successful treatment (8).

Following the optimistic results in patients with chronic hepatitis C, the same predictive factor was taken into evaluation in patients with chronic hepatitis B. In a study where the relationship between the virological breakthrough and the serum β-2 MG levels were investigated in HBeAg-negative patients who are under long term lamivudine treatment, it has been concluded that higher β-2 MG and HBV DNA levels in the third month of the treatment are a strong predictive factor for the virological breakthrough. Also, since the measurement of the serum HBV DNA levels both requires better established laboratory facilities and is more costly than the measurement of the β-2 MG levels, it has been suggested that the β-2 MG levels may show the way in the follow-up of the treatment and the determination of the treatment strategy (9). In the study by Akdogan et al. conducted on 53 patients where they investigated the relationship of the β-2 MG levels and the ALT exacerbation that develops during the treatment in patients undergoing interferon treatment due to chronic hepatitis B infection, the investigators have concluded that the β-2 MG level may be a predictive factor for the assessment of the treatment result before and during the treatment (10). In another study, a total of 65 patients including 19 inactive HBsAg carriers and 46 patients with chronic hepatitis B infection were investigated and the serum β-2 MG levels were found to be higher in the group with chronic hepatitis B infection in comparison to the inactive carriers and the control group. The study concluded that the β-2 MG levels may be an important parameter to start the interferon treatment at an early phase in chronic active hepatitis B patients (11). In our study, despite the significantly higher starting β-2 MG levels in the treatment group compared to the control group, a significant decrease was observed in the β-2 MG levels in the second month of the treatment.

In a study by De Man Ra et al. conducted on 36 patients with HBeAg-positive chronic hepatitis B infection, the relationship between the β-2 MG levels and the interferon treatment was assessed. Before the treatment, the β-2 MG levels were observed to be higher in 39% of the patients. At the fourth and eighth weeks of the treatment, a significant difference was observed in the β-2 MG and AST activity in the treatment group in relation to the control group. These parameters stayed stable in the control group. However, the average increase in the β-2 MG and AST levels before and during the treatment were observed to be comparable bet-ween the group with treatment response and the group without a treatment response. Thus, the antiviral treatment result was thought to be independent from the β-2 MG levels before and during the treatment (12). In a study by Beorchia et al., the increase in the β-2 MG levels in liver diseases has been investigated in 160 patients, 63 healthy controls and 75 asymptomatic HBsAg carriers. The β-2 MG levels of the control group and the asymptomatic carriers and were found within normal limits. Increased β-2 MG levels were observed in the patients with acute viral, chronic active and persistent hepatitis, as well as the cirrhotic patients. The β-2 MG levels in chronic persistent hepatitis patients were found to be significantly lower than the other three groups. These variations in the β-2 MG levels during the disease have been observed to be independent from the serum transaminase, bilirubin and gamma globulin readings. It has been concluded that increased β-2 MG levels are often observed during the active form of the inflammatory liver diseases (13).

In parallel to the difference observed between the starting β-2 MG levels in the treatment group and the control group, also similar to the above-mentioned study, no relationship was observed between the β-2 MG levels and the transaminases in our study. In a study conducted on a limited number of patients, the β-2 MG levels in patients with chronic hepatitis and cirrhotic HCC were observed to be higher. It has been suggested in the same study that the β-2 MG levels may be an important marker in determining the HCC (14).

In conclusion, the β-2 MG values may be useful parameters both to make the decision to start the treatment and in the follow up of the treatment success. However, since the number of the patients enrolled was limited, studying this parameter in larger patient groups seems necessary in order to establish an economic parameter to initiate and follow up this costly treatment modality.

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