Original Article

Persistent ALT Elevation in Chronic Hepatitis B Patients Entering to Remission with Treatment

Tedavi ile Remisyona Giren Kronik Hepati B Hastalarında Persistan ALT Yüksekliği

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Abstract

Aim: Our aim is to investigate the reason for persistent ALT elevation in chronic Hepatitis B (CHB) patients entering into remission with antiviral treatment.

Material Method: 10 patients with persistent ALT elevation were included in the study and their pre-treatment HBV-DNA values, serological tests, ALT, AST titers, liver fibrosis degree, ultrasonography (USG) and antiviral medicines they were taking were analyzed. While the time passed since the beginning of the treatment in these patients was evaluated, their HBV-DNA, serology, bio-chemical tests, other liver functions tests, serum cholesterol and triglyceride levels, liver USG, autoimmune tests and possible other hepatitis reasons were searched again.

Results: At the beginning of the treatment, HBV-DNA values of the 10 patients, all of whom were male, were between 10^4-10^8 copy/ml and 5 of the patients had HBeAg seroconversion. Considering virological response with treatment, HBV-DNA was 244 IU/ml in only one of the patients whereas it was negative in the rest and HBeAg seroconversion occurred in all the patients. It was realized that there was an increase in ALT values of five patients compared to pretreatment; ALT value remained the same in one of the patients and ALT values of the remaining four patients did not decrease to normal despite a decline. When liver USG was analyzed, no other pathology was determined except for the grade I hepatosteatosis in two patients. Other viral hepatitis agents and autoimmune hepatitis markers were negative, and liver functions tests and alpha-fetoprotein (AFP) were normal. In the patients' stories, there was no reference to quitting medicines, alcohol and drug use or taking other medicines that could be a cause. Considering the antiviral medicines the patients took, it was observed that four of the patients took entecavir, four of them took tenofovir, one took entecavir + tenofovir, one took telbivudin and one took Peg-Interferon.

Conclusion: ALT elevation of CHB patients may continue even if they are virologically and serologically in remission with treatment. This situation faces us as a problem which has no precisely known reason and needs highlighting.

Keywords: Chronic Hepatitis B, Remission, Alanine Transaminase

Öz.

Amaç: Amacımız, anti viral tedavi ile remisyona giren kronik hepatit B (KHB) hastalarında persistan ALT yüksekliğinin nedenini araştırmaktır.

Materyal Metod: Persistan ALT yüksekliği olan 10 hasta çalışmaya alınarak tedavi öncesi HBV-DNA değerleri, serolojik testleri, ALT, AST düzeyleri, histopatolojik olarak fibroz derecesi, ultrasonografisi, kullanmakta olduğu anti viral ilaçlar incelendi. Bu hastalarda tedavi başlangıcından itibaren geçen süre değerlendirildiği sırada hastaların yine HBV-DNA, seroloji,

biyokimyasal testler, diğer karaciğer fonksiyon testleri, serum kolesterol ve trigliserid düzeyleri, karaciğer ultrasonografisi, otoimmün tetkikleri ve muhtemel diğer hepatit nedenleri araştırıldı.

Bulgular: Tamamı erkek 10 hastanın tedavi başında HBV-DNA değerleri 10^4-10^8 kopya/ml arasında ve hastaların beşinde HBeAg serokonversiyonu vardı. Tedavi ile virolojik yanıta bakıldığında hastalardan sadece birisinde HBV-DNA 244 IU/ml iken, geri kalan kısmında negatifleşti. Ve hastaların tümünde HBeAg serokonversiyonu oluştu. Hastaların beşinde ALT değerlerinde tedavi öncesine göre yükselme olduğu; bir hastada ALT değerinin aynı kaldığı, geri kalan 4 hastada da ALT değerlerinde düşme olmakla beraber normale gelmediği görülmektedir. Karaciğer USG incelendiğinde iki hastada grade I hepatosteatoz dışında başka bir patoloji tespit edilmedi. Diğer viral hepatit etkenleri ve otoimmun hepatit markerları negatif olup karaciğer fonksiyon testleri ve alfa feto protein (AFP) de normal idi. Hastaların hikâyesinde ilacı bırakma, alkol ve madde (drug use) kullanımı veya neden olabilecek başka bir ilaç kullanımı da söz konusu değildi.Hastaların kullandığı antiviral ilaçlara bakıldığında dört hastanın entekavir, dört hastanın tenofovir, bir hastanın entekavir + tenofovir, bir hastanın telbivudin ve bir hastanın da pegile interferon alfa kullandığı görüldü.

Sonuç: KHB hastaları, tedavi ile virolojik ve serolojik olarak remisyonda olsalar bile ALT yüksekliği devam edebilir. Bu durum, nedeni tam olarak bilinmeyen ve aydınlatılması gereken bir sorun olarak karşımızda durmaktadır.

Anahtar kelimeler: Kronik hepatit B, Remisyon, Alanin transaminaz

Introduction:

Chronic Hepatitis B (CHB) still remains to be a problem in developing and underdeveloped countries. Though there is a preventive vaccination, its effects continue in some countries either because of lack of access to the vaccination or because of previous generations already infected with the virus.

It is predicted that there are still over 350 million people CHB patients all over the world. And approximately 1 million people die per year as a result of diseases related to Hepatitis B infection (1-5). It plays a role as the most common reason for liver cirrhosis and primary liver cancer (HCC) in many countries where it features endemically (6).

Currently, parenteral and oral anti-viral medicines are used in CHB treatment. It is suggested that parenteral treatment be used for a limited period while oral treatment should be used till HBsAg becomes negative (7,8).

Patients' response to the treatment is understood via virological (loss of HBV-DNA), serological

(HBsAg and HBeAg seroconversion) and bio-chemical (ALT normalization) tests. Whereas HBeAg seroconversion occurs at an important rate, HBsAg seroconversion occurs rarely. While persistent ALT elevation in CHB patients represents a failure in responding to the treatment, re-elevation of the decreased ALT implies development of resistance to the treatment.

Purpose of this study is to investigate the reason for persistent ALT elevation in CHB patients who respond to the treatment via entering into virological remission. Since there has been no previous study on this issue, as far as we searched; we would like to get clinicians' attention to this issue in order to untie the knot.

Material and Method

Of 2200 patients we followed in our clinic due to CHB, 98 patients taking antiviral treatment were investigated in this study. 10 of them who had persistent ALT elevation were included in the study, and their demographic features, pre-treatment HBV-DNA values, serological tests, ALT, AST levels, fibrosis degrees derived from liver biopsy results, liver ultrasonography (USG), anti-viral medicines they were taking and the commercial form of these medicines were analyzed. While the time passed since the beginning of the treatment in these patients was evaluated, their HBV-DNA, serology, bio-chemical tests, other liver functions tests, serum cholesterol and triglyceride levels, liver USG, autoimmune markers, other viral hepatitis reasons (hepatitis D virus, hepatitis C virus, Human immunodeficiency virus), Wilson disease, hemochromatosis tests were conducted, and biopsy was done for a second time to the patients who consented.

Patient	Age	HBV-DNA	HBeAg	Anti-HBe	ALT/AST	F	USG	Drug
1	35	10^8	Pos	Neg	**76**/30	2	Nrm	ETV (A^R)
2	42	10^8	Pos	Neg	**82**/60	4	Nrm	TDF (B^R) + ETV (A^R)
3	36	14.10^3	Neg	Pos	**63**/30	3	Nrm	ETV (C^R)
4	47	16.10^5	Neg	Pos	**110**/47	2	G II S	ETV (C^R)
5	51	10^7	Neg	Pos	**191**/113	3	G II S	TDF (D^R)
6	25	10^7	Neg	Pos	**92**/58	2	G I S	TDF (B^R)
7	38	10^7	Pos	Neg	**25**/23	3	Nrm	ETV (E^R)
8	25	10^8	Pos	Neg	**320**/158	2	Nrm	TDF (B^R)
9	44	8.10^5	Neg	Pos	**320**	4	Nrm	LdT
10	34	5.10^4	Pos	Neg	**327**/158	4	Nrm	Peg-Ifn

Table 1. Pretreatment values of patients.

Abbreviations

ETV: *Entecavir*
TDF: *Tenofovir*
LdT: *Telbivudin*
F: *Fibrosis*
Nrm: *Normal*
Pos: *Positive*
Neg: *Negative*
USG: *Ultrasonography*
(A^R), (B^R), (C^R), (D^R), (E^R): *Commercial forms of drugs*
G1 S: *Grade 1 steatoz*

Results

As seen in table 1, all the patients were male and the mean age was 37.7 ± 8.6 years. The lowest HBV-DNA value was 10^4 copy/ml whereas the highest value was 10^8 copy/ml. The ALT value in one of the patients was within normal limits, almost twice as high as the upper limit in two of the patients and more than twice as high as the upper limit in the rest of the patients. While HBeAg was positive and Anti-HBe was negative in five of the patients, HBeAg was negative and Anti-HBe was positive in the other five patients. In the liver USG analysis, there was grade II hepatosteatosis in two of the patients and grade I hepatosteatosis in one of the patients whereas the USG of the rest of the patients was normal. The anti-viral treatment that our patients took and their commercial forms are presented in table 1. The patients' values measured years after the treatment are shown in table 2. The time passed after the treatment ranged between 2 and 8 years. As the treatment of one of our patients had started outside our clinic, the length of his treatment was unknown. Considering the virological response, HBV-DNA was 244 IU/ml in only one of the patients whereas it was negative in the rest of the patients. HBeAg seroconversion occurred in all the patients with the treatment. With respect to the bio-chemical tests, it was realized that compared to pre-treatment, there was an increase in ALT values of some of the patients (1-4 and 7), the ALT value remained the same in one of the patients and the ALT values did not decrease to normal despite a decline in the remaining four patients. Moreover, HBeAg seroconversion and Anti-HBe positivity occurred in three of the patients (1, 2 and 7), whose ALT values displayed an increase. From the beginning of the treatment until now, persistent ALT elevation has consistently sustained to be high apart from slight increases and decreases. The pre-treatment liver fibrosis of the patients were between 2 and 4. However, the second biopsy has been done to only three patients until now, and the fibrosis in one of these patients was at the same degree while a decline was observed in fibrosis degree of the other two patients. Whereas there was grade II hepatosteatosis in two of the patients and grade I hepatosteatosis in one of them before the treatment, there was currently hepatosteatosis in only two of the patients and they were grade I. When the liver USG was analyzed, no other pathology was identified either before the treatment or at present. Other viral hepatitis agents added onto CHB and other infections were searched. HIV, HCV, HDV were negative and HAV was defeated. Also, brucellosis which was endemic in our region was found to be negative. Hemochromatosis and Wilson disease were searched but no positive result was found. Serum triglyceride and cholesterol levels were normal except for slightly high levels in two of the patients. Besides, other liver functions tests and

alpha-fetoprotein (AFP) were also within normal limits. Considering the possibility that the patients might have autoimmune hepatitis, Gamaglobulin/IgG, AMA, ASMA and LKM1 markers were examined; in addition, previous and current biopsies were re-analyzed through this perspective. However, no positive result was found in favor of autoimmune hepatitis. In the patients' stories, there was not any case of alcohol and drug use or taking other medicines that could give rise to it. Regarding the antiviral medicines that the patients took, it was observed that four of the patients used entecavir, four took tenofovir, one took entecavir + tenofovir, one took telbivudin and the other took Peg-Interfeton. When the commercial forms of the medicines were examined, it was realized that 5 different commercial forms were used (Table 1).

Table 2. The values of patients after remission with treatment

Patients	T.D/Y	DNA	HBeAg	Anti- HBe	ALT /AST	F	OIH	USG
1	8	**Neg**	Neg	**Pos**	**122**/50	**2**	Neg	G1 S
2	7	**Neg**	Neg	**Pos**	**92**/45	**2**	Neg	Nrm
3	3	**Neg**	Neg	**Pos**	**83**/36		Neg	Nrm
4	6	**Neg**	Neg	**Pos**	**126**/58		Neg	Nrm
5	6	**Neg**	Neg	**Pos**	**119**/76		Neg	Nrm
6	-	**Neg**	Neg	**Pos**	**92**/45		Neg	Nrm
7	4	**Neg**	Neg	**Pos**	**89**/41	**2**	Neg	Nrm
8	2	**244 IU/ml**	Neg	**Pos**	**56/27**		Neg	Nrm
9	6	**Neg**	Neg	**Pos**	**218**/91		Neg	G1 S
10	5	**Neg**	Neg	**Pos**	**90**/29		Neg	Nrm

TD/Y: *Treatment duration/Year*
OIH: *Otoimmun hepatitis*
G1 S: *Grade1 steatoz*
Nrm: *Normal*
Pos: *Positive*
Neg: *Negative*

Discussion

While following up our patients, we observed that ALT elevation continued despite virological remission in some of our patients. In our analysis, we determined that approximately 10 patients proceeded this way. Before the treatment, HBeAg was positive in five

of these patients and HBeAg seroconversion also occurred via the treatment. We investigated whether the patients took a break from the treatment and used alcohol, drugs or other medicines but we could not find any positive results. We searched for the added viral hepatitis (D, C, HIV) that might have been a cause and other infections (brucellosis, cyst hydatid…), Wilson disease, hemochromatosis and hepatosteatosis; we found negative results except for mild steatosis in two cases. Actually, these cases of steatosis were already present before the treatment and further decreased to grade I while they were grade II before the treatment. We thought if the patients might simultaneously be infected with autoimmune hepatitis. In addition to the patients' autoimmune markers, their first biopsy preparations and the new preparations of the 3 patients who had a biopsy for the second time were analyzed with consideration to autoimmune hepatitis and liver USG was repeated. Nevertheless, no reason could be found in favor of autoimmune hepatitis. We realized that ALT elevation still continued in the patients who were followed for a year. Apart from these, we thought of continuation of liver fibrosis or the possibility of stress as an intervening factor. The negativity of HBV-DNA in 9 of the patients and its regression to quite a low level and the occurrence of HBeAg seroconversion showed that there was a response to the treatment. Even so, we suggested the patients to conduct a second biopsy in order to confirm. Only 3 of the patients accepted the second biopsy suggestion. As a result of the liver biopsy, it was noticed that fibrosis was the same as the pretreatment (F2→F2) in one of the patients and decreased (declining F4→F2, F3→F2) in the other two patients. In the analysis, no noticeable stress factor that could explain the persistent ALT elevation was determined. Though it did not explain the persistent ALT elevation, the only positive finding we had was that all the patients were male. Nonetheless, almost 40 patients who were taking antiviral treatment were also male but they were not identified with ALT elevation. In addition to all these, it was also realized that compared to the pretreatment, the ALT values increased in five of the patients and remained the same in one patient. To explain this finding, we hypothesized that the antiviral medicines the patients used might be responsible for hepatotoxicity. In order to test this hypothesis, we would need to discontinue the medication and follow up but we could not dare it due to the risk of reactivation. As also shown in table 1, there was ALT elevation in the patients although they used different active ingredients and different commercial forms, which weakens the possibility of medicine-driven hepatotoxicity.

While persistent ALT elevation faces us as an unknown equation, we have searched for its negative impacts on the patients. When we review the literature, some studies have specified

that the purpose of the treatment was basically negativity of HBV-DNA and HBeAg seroconversion, and ALT elevation in these patients was not normal (11, 12). Furthermore, viral load has been regarded as an independent risk factor for cirrhosis and HCC in some studies (7, 13). Considering these studies, we have achieved our treatment goal because negativity of HBV-DNA and HBeAg seroconversion have been ensured in our patients. However, another study specified that the ultimate point in the treatment is the elimination of HBeAg and HBV-DNA from the blood and regression of ALT values to normal. Moreover, it was stated that the risk of complications reduces as ALT level decreases even within normal limits. In still another study, it was claimed that a gradient in ALT level was significantly associated with hepatocellular carcinoma risk (14, 15). As stated in this study, our patients might be under risk due to ALT elevation alone. But the fact that fibrosis degree was reduced in the second liver biopsy we carried out demonstrated that the mere ALT elevation in our patients was far from being a risk factor for cirrhosis and HCC. Despite this optimistic view, we still keep following our patients with virological, serological and liver functions tests done every 3 months, liver USG and AFP done in 6-12 months intervals because we do not know what kind of surprises we may encounter in the future.

After all this research and analysis, the reason for persistent ALT elevation could not be determined. As the ultimate finding, all the patients were male, and without any evidence, we suspect the hepatotoxic effect of the antiviral medicine, which had a low possibility.

In conclusion, the ALT elevation alone may continue in CHB patients even though they are virologically and serologically in remission with treatment. This situation faces us as a problem which has no precisely known reason and needs highlighting. I hope that the large number of studies that will be conducted in the future will highlight this issue.

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