V207I MUTATION: HOW DOES IT AFFECT CLINICAL COURSE IN CIRRHOSIS?

Case Report

V207I MUTASYONU: SİROZDA KLİNİK SEYRİ NASIL ETKİLER?

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ABSTRACT

Drug resistance is an important problem in the treatment of hepatitis B virus infection, especially in cirrhotic patients. We don't know the impact of all mutations which are occurring by selections of HBV variants during the treatment period. Here, we reported a patient diagnosed with HBV related cirrhosis and good clinical course even YMDD variants (L180M, M204I and additional V207I mutations) during the 8 years follow-up period of lamivudine treatment and HBV DNA became negative by additional adefovir dipivoxil therapy. This case showed V207I mutation has not associated with clinical deterioration in cirrhosis and adefovir dipivoxil is effective on V207I mutation.

Key words: *cirrhosis;V207I.*

ÖZET

Hepatit B infeksiyonunda, özellikle sirotik hastalarda ilaç direnci önemli bir problemdir. Tedavi sırasında HBV varyantlarının seleksiyonu ile oluşan mutasyonların hepsinin klinik önemini bilmiyoruz. Bu yazıda, sekiz yıllık lamivudin tedavisi sırasında gelişen YMDD mutasyonlarına (L180M, M204I ve üzerine eklenen V207I mutasyonu) rağmen iyi klinik seyirli ve eklenen adefovir dipivoxil tedavisi ile HBV DNA'sı negatifleşen, HBV'ye bağlı karaciğer sirozlu bir hasta sunulmuştur. Bu vaka, V207I mutasyonunun siroz seyrini kötü etkilemediğini ve adefovir dipivoxil'in tedavide etkili olduğunu göstermiştir.

Anahtar Kelimeler: *Siroz; V207I.*

INTRODUCTION

Antiviral drug resistance is an important problem during the treatment in chronic hepatitis B virus (HBV) infection, especially in cirrhotic patients. Emergence of drug resistance generally results in disease progression. The main mutation in tyrosine, methionine, aspartate, aspartate

(YMDD) motif of reverse transcriptase (rt) associated with lamivudine (LMV) resistance is rtM204I/V. The other mutations were also reported in published articles (rtM204I/V + rtL180M, rtM204I, rtV173L + rtL180M + rtM204V, rtL180I + rtM204I, rtQ215S + rtM204I/V ± rtL180M, rtI169T + rtV173L + rtL180M + rtM204V, rtA181T, rtT184S + rtM204I/V ± rtL180 and rtM204S + rtL180M) (1). In fact, we don't know the impact of all these mutations which are occurring by selections of HBV variants during the treatment period. Environmental factors, host factors, viral load and therapy can affect the balance of these HBV variants. Some of these mutations have no clinical significance by alone. For example, the rtL180M is the most common compensatory mutation and alone is insufficient to result in LMV resistance (2). Everyday, new mutations are detecting by the development of molecular techniques. Some mutations were detected outside active site of HBV polymerase (like V207I) and are associated with resistance to LMV in vitro (3). There are a few reports about V207I mutation in patients (4, 5). Zollner B et al (5) reported that the prevalence of V207I mutation was 1% in their study included 96 naïve patients. Here, we reported a patient diagnosed with HBV related cirrhosis and good clinical course even YMDD variants during the 8 years follow-up period of lamivudine treatment.

CASE REPORT

A-K 50 year's old man, he was following up from our out-patient clinic since 1999. He was diagnosed with HBV related cirrhosis by biochemical results, virologic analyses, clinical and liver biopsy findings. Physical examination revealed minimal ascites which was well controlled with diuretics, and splenomegaly. Serologic analyses were as follows: hepatitis B surface antigen (+), hepatitis B e antigen (-), antibody to hepatitis B e antigen (+), total antibody to hepatitis delta virus (-), antibody to hepatitis C virus (-) and HBV DNA 555 pg/ml (Hybride capture system, Digene corp., Gaithersburg, Md.). Gastroscopic examination revealed grade 3 esophageal varices. Laboratory results are shown on **table 1.**

	1999	2000	2001	2002	2003	2004	2005	2006
(IU/L)	54	27	23	114-53	60-121	72-39	38-76	34
(IU/L)	65	34	31	98-54	79-153	97-37	37-86	42
(IU/L)	97	94	239	242	199	207	234	214
(IU/L)	43	37	26	30	30	44	41	65
min/yglobulin(g/dl)	2.9/2	4.2/1.8	4.1/1.7	4.2/1.4	4.3/1.3	3.6/1.8	4/1.7	4/1.6
rombin time (sec)	17				16.7	14.8	16	16
bilirubin (mg/dl)	0.7			1.14	1.35	1.1	0.77	
let /mm^3	71000	98000	62000	50000	36000	42000		41000
DNA copy/ml	157065000	52638000			12452000		31200000	65484

Table 1: *Biochemical and virologic results during the follow-up period.*

He had followed up without treatment for one year in another hospital. After he was admitted to our out-patient clinic, LMV (100 mg/day, PO) were started because of high virologic load, aminotransferase activity and cirrhotic stage. After four years of lamivudine treatment, YMDD mutations were analyzed because of increased aminotransferase and HBV DNA levels. Results were revealed L180M, M204I, V207I mutations (Inno-Lipa Innogenetic kit, Belgium) and then adefovir dipivoxil 10 mg/day plus LMV 100 mg/day were received, and 3 months later lamivudine was stopped. We also retrospectively analyzed YMDD mutations from -85 °C stored serum samples **(Figure 1).**

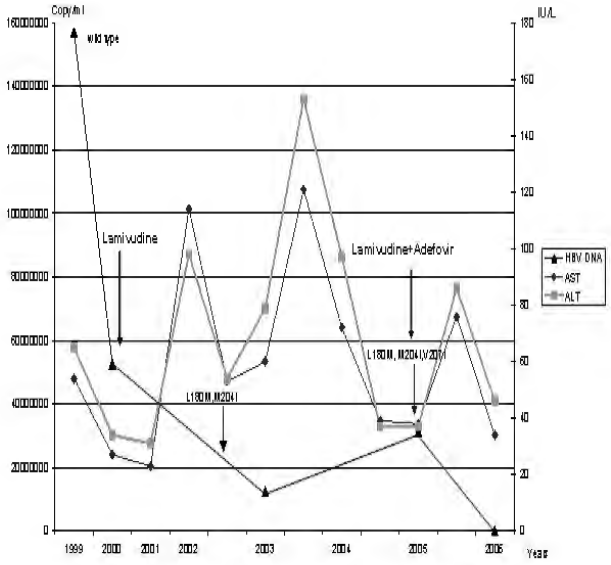

Figure 1: *Antiviral therapy and YMDD mutations with HBV DNA and aminotransferase levels during the follow-up period.*

Although, L180M, M204I mutations were detected in 2003. Therapy was not changed and LMV monotherapy was continued. Lamivudine resistance followed up with elevation of aminotransferases and HBV DNA levels. In spite of continuation LMV monotherapy, aminotransferase levels were decreased. Additional V207I mutation was detected in the last ALT flares period. But we did not observe clinical deterioration even the emergence of all resistance mutations. At one year of adefovir dipivoxil treatment HBV DNA was negative (bDNA Versant 3.0, Bayer Diagnostics, lower detection limit: 2000 copy/ml), and ADV resistance was not detected.

DISCUSSION

A retrospective analysis of patients infected with HBeAg-negative HBV strains, many of whom had severe liver disease at inclusion; found that viral breakthrough was associated with a higher probability of clinical deterioration (6). In our case, we did not observe serious HBV DNA flares associated with aminotransferase flares. HBV virus genome is complex and it has a dynamic structure. Many variants can be occurring during the years and some of them affects clinical course bad. Zollner B et al. (5) showed V207I mutation in a case who had HBV and HCV dual infection and they speculated that mutant's virus may have had an advantage over wild-type HBV because of inhibitory effects induced by HCV on HBV wild-type replication. HCV was not positive in our case. Child-Pugh score were also regressed even mutant variants become dominant. But, Zollner B et al. concluded that V207I mutation is associated with resistance to LMV in vitro but not in vivo (5). However, recurrence flares were observed after emerge of mutation and then supression of HBV DNA was obtained by adefovir dipivoxil therapy in our case.

In conclusion, V207I mutation has not associated with clinical deterioration in this cirrhotic patient, and it is a compensatory variant of HBV polymerase. This case also showed that adefovir dipivoxil is effective on V207I mutation.

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