Hepatitis B virus (HBV) infections are a major public health problem. It is estimated that there are more than 350 million HBV carriers in the world, of whom one million die annually from HBV-related liver disease [1]. Chronic hepatitis B may cause cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) resulting in significant morbidity and mortality. For this reason the main goals of chronic hepatitis B treatment are a sustained reduction of HBV DNA, biochemical remission, and histological improvement in order to prevent disease progression and long-term complications such as HCC [2].

Tenofovir disoproxil fumarate (tenofovir DF), the oral pro-drug of tenofovir, is a nucleotide reverse transcriptase inhibitor that shows potent in vitro activity against both HBV and immunodeficiency virus (HIV-1) [3]. Tenofovir DF was recently approved by the United States Food and Drug Administration (FDA) for the treatment of chronic HBV infections in adults. Tenofovir has a high genetic barrier and potent viral suppressive effect [4]. Its viral suppression ability in the first weeks after the initial treatment may be important in conditions where urgent viral reduction is necessary.

The present study investigated the viral suppression rate sequentially after starting tenofovir treatment. The factors affecting the rapid viral response are also evaluated.

This was a prospective trial that recruited patients from the Department of Gastroenterology, School of Medicine, Marmara University between 2008 and 2009. Sixteen patients (Male (n=10), Female (n=6), mean age: 46.9 ± 12.5) with chronic hepatitis B were enrolled in the study and treated with tenofovir (Table I). The median modified histological activity index (HAI) score for the initial liver biopsy was 7.166±5.166. The basal fibrosis stage of the patients was 0 (n=7), 1 (n=7) and 3 (n=2).

The patients were diagnosed with chronic hepatitis B using virological, biochemical, and histological parameters. Patients with coexisting hepatitis C, hepatitis D, HIV infection, evidence of hepatocellular carcinoma, decompensated liver disease, or significant renal comorbidity were excluded from the study.

Before starting the tenofovir treatment, a detailed physical examination, baseline liver enzyme tests, renal function tests, HBV DNA (TaqMan) measurements, and liver biopsies were carried out, and following the start of tenofovir treatment, weekly outpatient visits included a physical examination, liver enzyme tests, HBV DNA at weeks 2 and 4, followed by monthly follow-up visits testing the same parameters for 12 months.

Quantitative HBV DNA levels were measured using the Taqman PCR method. Patients with HBV DNA levels > 6 log were defined as high viral load patients, whereas < 6 log units were defined as low viral load patients. HBeAg status, baseline alanine aminotransferase (ALT) (High ALT 5x upper limit of normal (ULN)), age, gender, and exposure to prior treatment were evaluated for response rates.

The statistical analysis was performed by General Linear Models Repeated Measures and Pillar’s Trace test. In pairwise comparisons Bonferroni test was used. Complete treatment response was defined as HBV DNA < 400 copies/ml.

Of the 16 patients enrolled, ten had previously been treated with lamivudine, interferon or/and adefovir, the other six were naive patients.

The mean HBV DNA levels at baseline and after 2 weeks, 1, 2, 3, 4, 5, 6, and 12 months were 6.063 ± 1.6 log, 3.438 ± 1.5 log, 2.813 ± 1.6 log, 2.375 ± 1.6 log, 1.688 ± 1.6 log, 1.688 ± 1.6 log, 1.5 ± 1.4 log, 1.25 ± 1.2 log, 0.75 ± 1.055 log respectively (Fig 1). A large and rapid decline (3 log units) was seen in the first 2 weeks, followed by slower rates of decline in the following months. The HBV DNA decline was statistically significant (p <0.001).

There was no difference in the rates of decline between patients with either a high or low viral load. However, patients with a low viral load reached one log unit of HBV DNA level more rapidly (in 3 months vs. 6). However, the rate of ALT decline was slower than the rate of HBV DNA.
decline, and ALT normalization occurred at month 6 (Fig 2). ALT decline was statistically significant (p<0.05). Age, gender, prior treatment, and baseline ALT levels had no effect on viral decline and ALT normalization rates.

This study shows that tenofovir has a potent viral suppression effect and causes rapid viral decline in the first two weeks of treatment, and this enhances the understanding of the early viral kinetics of tenofovir.

In several studies on HBV-infected patients, the majority with a lamivudine-resistant virus, tenofovir resulted in a reduction of 4 to 6 log copies/ml in serum HBV DNA level from baseline over 48 weeks and in the reduction of 5 log copies/ml compared with a placebo; in addition HBV DNA was undetectable by PCR assay in 30-100% of patients after more than 24 weeks of treatment [5].

In the study of Heathcote et al HBeAg(+) subjects were randomized to receive tenofovir (N=176) or adefovir (N=90) for the first 48 weeks; after 48 weeks they either remained on tenofovir or were switched from adefovir to tenofovir for an additional 3 years [6]. At week 72, data demonstrated that 79% of patients who had originally been randomized to receive tenofovir and 76% of switched patients had < 400 copies/ml HBV DNA. Additionally, switching to tenofovir after 48 weeks of adefovir treatment caused significant viral suppression in 78% of patients with HBV DNA levels above 400 copies/ml [7]. The same study with HBeAg (-) patients showed similar results [8]. Tenofovir showed superior efficacy over adefovir in the treatment of chronic hepatitis B [7,8]. In these studies, HBV DNA levels were assessed for baseline levels every 4 weeks.

In our study we also analyzed HBV DNA levels at week 2. A large and rapid decline (3 log units) was seen in the first 2 weeks, followed by slower rate of decline in the following months.

The rapid effect of tenofovir has been shown previously for both HIV and HBV treatments. In the study of van der Eijk et al 11 chronic HBV infection patients who developed YMDD mutation–related HBV-DNA breakthrough on lamivudine therapy for a median of 176 weeks received add–on tenofovir 300 mg/day, while maintaining existing therapy. The viral decay in the first week (first-phase) and in the following 23 weeks (second-phase was investigated). It was shown that after an initial rapid decline in viral load in the first-phase, the response in the following weeks was highly variable between individual patients. The authors concluded that the rapid first phase of the decline reflects the clearance rate of free virus from the plasma; the second-phase decline reflects the death rate of productively infected cells [9].

There are potential limitations to the current study. The limited number of patients that were enrolled to the study is one, and the other is that we did not evaluate the viral kinetics

<table>
<thead>
<tr>
<th>Table 1. Demographic characteristics of the patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>AST(IU/L) (Mean± SD)</td>
</tr>
<tr>
<td>ALT(IU/L) (Mean± SD)</td>
</tr>
<tr>
<td>HBV DNA (log) (Mean± SD)</td>
</tr>
</tbody>
</table>

AST: aspartate aminotransferase, ALT: alanine aminotransferase, HBV: hepatitis B virus
according to the HBV genotype. However, we have shown that more than 90% of patients are genotype D in the Turkish population [10]. On that basis, we can clearly say that most of those patients probably had genotype D.

In conclusion, tenofovir causes a rapid viral decline in the first 2 weeks of treatment in patients with both high and low viral loads. Thus, tenofovir can be regarded as a good choice for patients where rapid viral decline is needed. The rapid and potent antiviral efficacy of tenofovir makes it an attractive rescue therapy for patients with liver cirrhosis and liver decompensation. In addition, a greater and more rapid reduction in HBV DNA levels may result in more prolonged efficacy and less risk of viral resistance.

References