Cost of Treatment in HBeAg-Negative Chronic Hepatitis B Patients with 10-Years Projection Analysis

HBeAg Negatif Kronik Hepatit B Hastalarında Tedavi Maliyetlerinin 10 Yıllık Yansıtma ile Analizi

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Abstract

Objective: Chronic hepatitis B infection has to be treated effectively due to its major complications. The aim of this study is to investigate and compare the therapy alternatives’ treatment costs for hepatitis B e antigen (HBeAg) negative patients with 10-year projection analysis according to current reimbursement guideline in Turkey.

Materials and Methods: All testing that should be done before the treatment and during follow-up was determined according to the guideline. Medicinal costs were calculated according to 2014 prices. Cost calculation was performed on 100 hypothetical HBeAg negative, 35 years old patients whose alanine aminotransferase value was >2 X upper limit of the normal laboratory level by taking into consideration the risks of resistance seen during the treatment. Switching to tenofovir scenario was concocted when resistance to lamivudine and telbivudine was developed. In pegylated-interferon non-responders, alternative scenarios have been edited and evaluated.

Results: The total cost of patients whose treatment was started with pegylated-interferon and switched to lamivudine and tenofovir due to non-response was found 2,662,504 TL. Treatment cost of patients whose therapy was passed to tenofovir after initiation with lamivudine or telbivudine was 2,444,175 TL and 3,061,869 TL, respectively. From the beginning of treatment in patients taking entecavir or tenofovir, the 10-year cost of treatment was 3,924,960 TL and 3,884,040 TL, respectively.

Conclusion: As a result, when assessing the cost of the treatment of chronic hepatitis B not only medicine box costs, but also drug resistance and laboratory testing costs, should be considered. In our country, on the basis of 10 years cost; pegylated-interferon and lamivudine therapy has been found advantageous in patients with low viral load, and tenofovir has been found advantageous in patients with high viral load.

Keywords: Pharmacoeconomy, antiviral, hepatitis B, cost of treatment

Özet

Amaç: Kronik Hepatit B enfeksiyonu ciddi komplikasyonlara neden olduğu için mutlaka tedavi edilmelidir. Bu çalışmanın amacı, hepatit Be antijen (HBeAg) negatif hastalardaki tedavi alternatiflerinin maliyetlerini mevcut geri ödeme kilavuzuna göre 10 yıl projeksiyon analizi ile araştırmak ve karşılaştırmaktır.


Sonuç: Kronik hepatit B enfeksiyonu tedavi maliyetleri değerlendirildiği için sadece ilaç kutu maliyetleri değil, ilaç direnci ve laboratuar test maliyetleri de değerlendirilmeliidir. Ölçükte düşük viral yük olan hastalarda 10 yıl baz alındığında pegile-interferon ve lamivudin teda-vileri avantajlı bulunmuş iken yüksek viral yükü hastalarda tenofovir tedavi maliyeti olarak avantajlı bulunmuştur.

Anahtar Kelimeler: Farmakoekonomi, antiviral, hepatit B, tedavi maliyeti

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Introduction

Hepatitis B virus (HBV) infection continues to be the one of the most prominent and problematic health problems. All over the world, it is forecasted that there are 350 million active HBV carriers and approximately 500,000 deaths caused by HBV [1, 2]. Around one third of the world’s population is infected with HBV, again one third of the cirrhosis cases and half of the hepatocellular cancer cases are caused by HBV. Chronic hepatitis B (CHB) infection has to be treated effectively due to its major complications like (cirrhosis, HCC and mortality) [3]. Agents used to treat Chronic HBV are: Interferon alpha (IFN), Lamivudine (LAM), Adefovir, Entecavir (ETV), Pegylated interferon alpha (PEG-IFN), Telbivudine (TLB) and Tenofovir (TFV) and their launch dates are as follows: 1991, 1998, 2002, 2005, 2005, 2006 and 2008 [4].

Lamivudine is the first oral antiviral launched and also used in Turkey. According to last updated reimbursement guideline, for hepatitis B e antigen (HBeAg) negative patients who have HBV-DNA level between 2000-2,000,000 IU/mL can be treated either with IFNs if they have (ALT >2 X upper limit of the normal lab level) or with NAs like LAM and TLB. On the other hand, if patients have HBV-DNA level over 2,000,000 IU/mL, these patients are allowed to treat with ETV or TFV [5].

The most important advantages of Interferon treatment are: finite course of therapy, dual mode of action - antiviral and immune modulatory effects and no drug resistance reported. While the duration of IFN therapy is 48 weeks, duration of the therapy for oral antiviral agents is depending on patients’ HBeAg status. For HBeAg positive patients, one more year of antiviral therapy is recommended after HBeAg seroconversion and after one year additional antiviral therapy it is recommended to stop the treatment. For HBeAg negative patients, antiviral therapy is recommended to continue until hepatitis B surface antigen (HBsAg) loss [6].

All major guidelines acknowledge the importance of HBsAg clearance as the ideal endpoint in the treatment of CHB but it is rarely attainable. Therefore antiviral therapy is life-long for most of the cases. For this long time interval there are alternative therapy regimens due to HBV DNA levels. While patients’ conditions and characteristics like renal function are important features to choose the antiviral agent as treatment, alternative treatment costs are other important features to choose the antiviral agents. Treatment cost issue for HBeAg negative patients has not been calculated accurately due to long and ill-defined therapy duration. The purpose of this study is to investigate and compare the therapy alternatives’ treatment costs and the results of these costs for HBeAg negative patients with 10-Year Projection Analysis according to current reimbursement guideline in Turkey.

Materials and Methods

Patient Monitoring Treatment Costs

This cost has been calculated by concerning one patients required tests for the monitoring for the whole therapy duration in parallel with the reimbursement guideline (HBsAg quantification, biopsy, upper abdominal ultrasound findings, HBsAg, HBeAg, AntiHBe, HBV-DNA quantity, Anti-HDV, Anti-HCV, alanine aminotransferase, aspartate aminotransferase, gama-glutamyltranspeptidase, WBC, total bilirubin, direct bilirubin, indirect bilirubin, urea, creatinine, albumin, alpha-fetoprotein, total protein) [4].

Medicinal Costs of Agents Used in Chronic HBV Therapy

Medicinal costs calculated according to 2014 prices (Table 1).

Patient scenarios

In this projection hypothetical 100 patients whose HBeAg (-), at age of 35 and ALT >2 X upper limit of the normal laboratory level have been evaluated according to the treatment costs. Considering the drug resistance rates reported in the researches, the costs of switching from one therapy to other therapy has been calculated also. Base scenario for LAM & TLB resistance was switching to TFV. Alternative scenarios for the IFN non-responders had been identified and evaluated.

Calculation

For each scenario, an alternative therapy regimen was chosen in case of drug resistance in line with the therapy guidelines. New therapy costs added to the former costs.

### Table 1. Retail and public discounted prices for chronic Hepatitis B treatment drugs

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Price</th>
<th>Discount</th>
<th>Public Price</th>
<th>Public Paid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegylated interferon</td>
<td>362.39 TL</td>
<td>17%</td>
<td>300.78 TL</td>
<td>300.78 TL</td>
</tr>
<tr>
<td>Entecavir 0.5 mg</td>
<td>448.99 TL</td>
<td>28%</td>
<td>323.27 TL</td>
<td>300.95 TL</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>413.25 TL</td>
<td>28%</td>
<td>297.54 TL</td>
<td>297.54 TL</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>89.43 TL</td>
<td>28%</td>
<td>64.39 TL</td>
<td>64.39 TL</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>421.34 TL</td>
<td>63%</td>
<td>155.90 TL</td>
<td>155.90 TL</td>
</tr>
</tbody>
</table>
For the drug resistance rates guideline data were chosen as the benchmark. For the Interferon therapy success, genotype D response rates were used as baseline. Calculations were made on monthly and yearly bases.

### Results

The total cost for PEG-IFN therapy scenario was calculated as 2,662,504 TL. In this scenario PEG-IFN was given as the first line therapy and then at the 3rd week non-responders are excluded and these patients were given LAM or TFV (Table 2). The total cost for LAM therapy scenario was calculated as 2,444,175 TL. In this scenario LAM was given as first line therapy and then at month 6 LAM resistance patients were given TFV (Table 3). The total cost for TLB therapy scenario was calculated as 3,061,869 TL. In this scenario TLB was given as the first line therapy and then TLB resistance patients were given TFV (Table 3). ETV and TFV were calculated as follows given the patients’ 10 years total treatment costs: 3,924,960 TL and 3,884,040 TL (Table 4). Each drug’s one year treatment costs were given in Table 5. According to these findings one year cost of PEG-IFN was the most expensive one and one year cost of LAM was the lowest. In terms of ten years treatment costs, the highest cost belonged to ETV, on the other hand, the lowest cost belonged to LAM treatment (Figure 1).

### Discussion

In this article, 10 years treatment costs for Chronic HBV were evaluated on the basis of reimbursement guideline price list. In ten years’ evaluation, ETV and TFV treatment costs were highest and LAM treatment cost was the lowest among the alternative therapies.

Hepatitis B virus infected patients’ mortality rate are 3.6 times higher than the normal population due to liver associated diseases. These patients should be given immediate therapy in order to increase their life expectancy, quality of life and to protect from complications like cirrhosis, HCC. However, while deciding on the therapy, alternative treatment costs should be considered [7].

Lamivudine is considered as the cheapest alternative among the oral antivirals. On the other hand, LAM treatment can only be prescribed under 2,000,000 IU/mL HBV-DNA level
due to its low antiviral potency and high resistance profile defined in the Health Practices of Notification. According to our findings, LAM can be an alternative treatment in low HBV-DNA level patients. But, after six months treatment with LAM mutants emerges, and in first year of therapy 15% resistance rate can be identified. Related to the viral load at the year five this rate reaches to 70%. For this reason, the main hurdle to start a LAM therapy is the high resistance rate [8].

The resistance problem plays an important role in managing the TLB treatment. Resistance rates at the end of one year and two years therapy with TLB were 4.4% and 21%, respectively. Besides, TLB treatment cost is higher than the LAM option [7]. TLB is not recommended as first line therapy in some of the guidelines due to low cost affectivity of this treatment [9]. When basing a 10 year cost in this study, the TLB cost was not found rational.

Within the European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD) and National Institute for Health and Clinical Excellence (NICE) guides, the PEG-IFNs are still offered as an important option among other first treatment options. The interferons take effect through antiviral, antiproliferative and immunomodulatory ways. While the interferons treatment success is high in Genotype A, it is as low as 17% in Genotype D, which is the most common genotype in our Country. The success rate that is aimed for is; for the HBV-DNA levels to drop under the 2000 IU/mL level by the end of the treatment [10]. In other words getting the patients inactive HBV to a state of infection is considered a treatment success [6]. Taking into consideration a yearly cost for the interferon treatment even though the cost seems high, when compared to a 10 year cost, it is comparatively lower. Furthermore, it is now possible to stop the treatments that seem to be failing in the third month by evaluating the HBV-DNA, quantitative and HBsAg results. This is why before leaving patients with the load of having to take oral antivirals for years, it is important to remember that the interferon is a good alternative for suitable cases.

Our study has some limits. When making a 10 year reflection, long term results such as cirrhosis, hepatocellular carcinoma and mortality were not taken into evaluation. Our study was only designed as year only reflections with treatment costs. Due to this, we cannot exactly say that our data shows the exact cost-effectiveness.

In conclusion, when evaluating the CHB treatment costs, not only the drug cost per box but the drug resistance and

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Regular Cost</th>
<th>Reimbursement Cost</th>
<th>1 Month treatment Cost</th>
<th>3 Month Treatment Cost</th>
<th>6 Month Treatment Cost</th>
<th>1 Year Treatment Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegylated interferon</td>
<td>362,39 TL</td>
<td>300,78 TL</td>
<td>1,203,12 TL</td>
<td>3,609,36 TL</td>
<td>7,218,72 TL</td>
<td>14,437,44 TL</td>
</tr>
<tr>
<td>Entecavir 0.5 mg</td>
<td>448,99 TL</td>
<td>300,95 TL</td>
<td>323,27 TL</td>
<td>902,85 TL</td>
<td>1,805,70 TL</td>
<td>3,611,40 TL</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>413,25 TL</td>
<td>297,54 TL</td>
<td>297,54 TL</td>
<td>892,62 TL</td>
<td>1,785,24 TL</td>
<td>3,570,48 TL</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>89,43 TL</td>
<td>64,39 TL</td>
<td>68,99 TL</td>
<td>206,97 TL</td>
<td>413,94 TL</td>
<td>827,87 TL</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>421,34 TL</td>
<td>155,90 TL</td>
<td>167,04 TL</td>
<td>501,11 TL</td>
<td>1,002,21 TL</td>
<td>2,004,43 TL</td>
</tr>
</tbody>
</table>

**Table 5. The first one year cost for Chronic Hepatitis B drugs**

**Figure 1. The 10 years cost graphic for the Chronic Hepatitis B treatment.**
the laboratory testing costs should also be considered. It is found that with a base of 10 years, while the PEG-IFN and LAM treatment advantages are low for patients in our country with low viral loads, the TFV treatment cost is found as an advantage with patients with high viral loads.

**Ethics Committee Approval:** Ethics committee approval was not received due to the nature of this study.

**Informed Consent:** Informed consent was not received due to the nature of this study.

**Peer-review:** Externally peer-reviewed.

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**Conflict of Interest:** No conflict of interest was declared by the authors.

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