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Research Article

ASSESSMENT OF INTERFERON, PEGINTERFERON, TENOFOVIR, ENTECAVIR, LAMIVUDINE AND ADEFOVIR FOR THE TREATMENT OF CHRONIC HEPATITIS B IN HBEAG-POSITIVE PATIENTS WITHOUT CIRRHOSIS

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ABSTRACT

Infection with the hepatitis B virus (HBV) is an important problem facing healthcare systems. Treatment aims to stop the progression of the disease. In Brazil, treatment for hepatitis B has universal funding from the Unified Health System (Sistema Único de Saúde, SUS). An economic evaluation of the treatment choices for chronic hepatitis B in HBV surface antigen (HBeAg)-positive patients without cirrhosis was performed, as requested by the director of the SUS. Objective: To analyse the cost-effectiveness of the drug treatment regimens for chronic hepatitis B.

Methods: A Markov model was developed to estimate the costs and benefits of the different treatment options. The SUS perspective was adopted to estimate the costs, and the benefits were measured in quality-adjusted life years (QALYs). The following therapeutic options, which include the drugs that are offered by the SUS for the treatment of hepatitis B, were evaluated: 1) interferon alpha; 2) peginterferon alfa-2a; 3) peginterferon alfa-2b; 4) tenofovir; 5) entecavir; 6) lamivudine; and 7) adefovir.

Results: Among the drugs, lamivudine was the most cost-effective strategy (US $462/QALY) followed by tenofovir.

Conclusions: Other Markov chain models of antiviral treatments for hepatitis B have indicated that tenofovir is the most cost-effective strategy; however, lamivudine was the most cost-effective therapy in this study. The lack of conclusive data on the efficacy of several drugs that are used to treat chronic hepatitis B is a limiting factor for the development of more robust studies.

Keywords: HBeAg reagents, Chronic hepatitis B, Cost-effectiveness, Lamivudine

INTRODUCTION

Hepatitis B virus (HBV) infection is an important problem for healthcare systems. Determining the prevalence of HBV infection and its potential for causing chronic disease is difficult, and treatment with variable rates of effectiveness is costly. Chronic disease affects approximately 10% of HBV-infected individuals [1] and results in approximately one million deaths annually; therefore, chronic HBV infection is ranked 10th in the index of causes of death worldwide [2-6].

A diagnosis of chronic HBV infection is based on the identification of antigens, antibodies and viral fragments, which can be used as markers of response to treatment. The lack of symptoms during the early stages of the disease complicates its identification, and a diagnosis is often made after there is significant liver involvement [7,8].

There is little consistent information on the prevalence of HBV infection in Brazil; however, it is estimated that 1% of the Brazilian population has a chronic disease that is related to HBV [9]. Treatment is directed at patients with signs of viral activity and liver damage and aims to stop the natural progression of the disease, thus preventing severe hepatic dysfunction and its consequences [10,11].

In Brazil, treatment of HBV has universal funding from the Unified Health System (Sistema Único de Saúde - SUS). Treatment of the infection is based on a clinical protocol that was designed according to a consensus of specialists. According to the Brazilian Ministry of Health, the sustained absence of the surface antigen of HBV (HBeAg) is the primary measure of the effectiveness of treatment [3].

An economic evaluation of the treatment options for chronic HBV infection in HBeAg-positive patients without cirrhosis was performed to analyse the cost-effectiveness of the treatment regimens that were proposed by the clinical protocol [3] according to the SUS. The patients in this study were selected because of their prevalent chronic HBV infections and because these patients are more clinically relevant than other types of patients.

Seven drugs currently available as therapeutic options for HBeAg-positive adults with hepatitis B and without cirrhosis were compared: 1) interferon alpha; 2) peginterferon alfa-2a; 3) peginterferon alfa-2b; 4) tenofovir; 5) entecavir; 6) lamivudine; and 7) adefovir.

METHODS

A Markov model of health state transitions that represented the progression of hepatitis B over annual cycles was developed to estimate the costs and benefits of the therapeutic approaches to the disease. The SUS perspective was used to estimate the costs, and the benefits were measured in quality-adjusted life years (QALYs). The time horizon was 30 years. The cost comparison between the drugs was conducted using the incremental cost-effectiveness ratio (ICER). A discount rate of 5% was applied to the costs.

Decision analysis software was used for the analysis of the cost-effectiveness (DATA, version 1.3.1, Tree Age Software, Inc., Williamstown, MA, USA) [12]. A hypothetical cohort of 1,000 male individuals was designed. These individuals were 40 years of age, HBeAg-positive, without cirrhosis and on different therapeutic regimens based on the drugs in the protocol. The probabilities of transition among the states of health in hepatitis B progression are listed in Table 1.

The disease progression was modeled using 12 states of health. The target population was HBeAg-positive patients without cirrhosis.

The Markov states progressed annually and included histological stages, which were defined according to the METAVIR criteria, and long-term complications of the infection, including compensated cirrhosis, decompensated cirrhosis, primary hepatocellular carcinoma and liver transplantation [3,13,14].

The therapeutic options that were provided by the SUS for the treatment of hepatitis B were evaluated. These options and their costs are listed in Table 2.

Table 1: Probabilities of transition among the states of health in hepatitis B progression.

Health state	p – (intervals for the sensitivity analysis)
Chronic HBeAg-positive disease	45 (0-100)
Chronic hepatitis to hepatocellular cancer	1.5 (0-10)
Annual progression to compensated cirrhosis in HBeAg-positive patients	3 (0.5-11)
Annual rate of mortality in compensated cirrhosis patients	4.9 (2-14)
Annual rate of progression from compensated cirrhosis to decompensated cirrhosis	7.3 (3.5-10)
Probability of developing ascites during the cirrhotic state	68 (50-90)
Probability of developing variceal bleeding during the cirrhotic state	14.6 (7-30)
Probability of developing encephalopathy during the cirrhotic state	10 (5-30)
Annual rate of mortality in decompensated cirrhosis patients	19 (6-25)
Annual rate of progression from cirrhosis to hepatocellular cancer	3.4 (1-12)
Annual rate of mortality in hepatocellular cancer patients	43.3 (20-60)
Annual rate of liver transplants during decompensated cirrhosis	25 (0-40)
Annual rate of liver transplants during hepatocellular cancer	30 (0-40)
Annual rate of mortality after a successful liver transplant	6.9 (2-12)

Source: [13]

Table 2: Drugs used for the treatment of hepatitis B and the treatment regimens.

Drug	Dose	Duration/Weeks	Cost* (US$)
Interferon alpha-2b	5 to 10 MIU 3x/week	16-24	600.00-1,482.35
Peginterferon alfa-2a	180 mcg 1x/week	48	21,240.94
Peginterferon alfa-2b	120 mcg 1x/week	48	25,554.82
Entecavir	0.5 mg/ day	52	1,653.64
Adefovir	10 mg	48	1,026.11
Lamivudine	100 mg/ day	48	130.11
Tenofovir	300 mg	48	662.12

Source: Calculated by the authors using data from 'ComprasNet' for each bid [15]. The period of validity for the bids was 2010/2011.

*The cost was calculated based on the lowest price found. The treatment times were 48 weeks for analogous nucleotides, nucleosides and peginterferons and 24 weeks for conventional interferons.

The U.S. dollar exchange rate on 05/10/2012 was R$2.04.

The protocol suggests that interferon alpha-2a or -2b are the drugs of choice for the treatment of non-cirrhotic HBeAg-positive patients, and the protocol indicates that tenofovir is a rescue option for nonresponsive patients. Entecavir can be used according to the discretion of the doctor. The other drugs can be used to treat co-infections with other viruses, particularly hepatotropic viruses. Because of perceived uncertainties in the protocol, the model tested the cost of treating the disease by considering each drug as an initial choice and not a secondary treatment in case of therapeutic failure.

A literature review was conducted to determine treatment effectiveness. The search included studies published up to 2011 that investigated the effectiveness of drugs used to treat naive hepatitis B patients who were HBeAg-positive. The data that were derived from these studies were included in the model. The response rates and the references to the studies are listed in Table 3. For several drugs, multiple outcome measures were found. In these cases, the best response rate was included in the model, and the worst rate was included in the sensitivity analysis. The adverse effects that were reported for each drug were not considered.

Table 3: Probability of response to therapy with drugs used to treat hepatitis B (end of treatment) according to selected studies.

Drug	Probability (%)	Reference
Adefovir	12	[16]
Adefovir	18	[17]
Entecavir	21	[18]
Interferon alpha-2b	27	[19]
Lamivudine	18	[18]
Lamivudine	20	[20]
Peginterferon alfa-2a	27	[19]
Peginterferon alfa-2b	22	[21]
Tenofovir	21	[17]
Probability of response to follow-up therapy with drugs used to treat hepatitis B according to selected studies.		
Drug	Probability (%)	Reference
Entecavir	77	[30]
Interferon alpha-2b	19-35	[22]
		[19]
Lamivudine	19-72	[29]
		[30]
Peginterferon alfa-2a	32-33	[29]
		[23]
Peginterferon alfa-2b	29	[21]

Table 4: Utility of the health states of hepatitis B.

Health state	Utility data	Interval
Ascites	0.65	0.35-1.0
Refractory ascites	0.65	0.35-1.0
Cirrhosis	0.82	0.46-1.0
Hepatocarcinoma	0.55	0.15-1.0
Gastrointestinal bleeding	0.53	0.19-1.0
Variceal bleeding	0.55	0.23-1.0
Moderate hepatitis	0.98	0.92-1.0
End of hepatitis treatment	0.92	0.72-1.0
Liver transplantation	0.86	0.66-1.0

Source: Prepared by expert consensus (Delphi panel).

The benefits were measured in QALYs; therefore, estimates of utility were constructed for the health states in the model. For this purpose, experts (the Delphi panel) were consulted, and the results of the consultation are shown in Table 4.

To test the robustness of the model and its approximation to reality, univariate sensitivity analyses were performed. The annual discount rates, the cost of drug therapy and the probability of response to treatment at the end of monitoring were subject to variation. These parameters were selected because they had the greatest potential impact on the final outcomes of the model.

RESULTS AND DISCUSSION

Analysis of cost-effectiveness

An analysis of the cost-effectiveness of the therapies used for treating chronic hepatitis B in HBeAg-positive patients was performed as requested by the SUS. The outcomes of interest were the presence of anti-HBe antibodies at the end of treatment and a sustained viral response (SVR) one year after the end of treatment. Patients who did not respond to treatment followed the natural progression of the disease. The results of the analysis are listed in Table 5.

Table 5: Cost-effectiveness of drugs used to treat hepatitis B.

Strategy	Cost (US$)*	Incremental Cost (US$)	Effect (QALY)	Incremental Effect (QALY)	C/E (US$/QALY)	ICER-US$/QALY
Lamivudine	5,606	0	12.124	0	462	
Tenofovir	6,032	425	12.192	0.068	495	6.293
Natural History	6,281	250	11.545	-0.647	544	(Dominated)
Entecavir	7,023	992	12.192	0.000	576	(Dominated)
Adefovir	7,197	1,165	11.689	-0.503	616	(Dominated)
Interferon alpha-2b 10 MUI	7,564	1,532	11.746	-0.446	644	(Dominated)
Peginterferon alfa-2a	27,042	21,010	11.93	-0.262	2,267	(Dominated)
Peginterferon alfa-2b	31,500	25,468	11.834	-0.358	2,662	(Dominated)

Source: Developed by the authors; *ICER=Incremental cost-effectiveness ratio.

Because of the lack of information about the response to tenofovir at the end of treatment, the response was suggested to be identical to that obtained with entecavir based on the study by Woo et al. (2010) [24], which demonstrated that tenofovir was more effective than entecavir. This limitation may affect our findings on the performance of tenofovir; however, the drug is more cost-effective than entecavir.

Among the drugs that were compared (interferon, peginterferon alfa-2a and -2b, tenofovir, entecavir, lamivudine and adefovir), lamivudine therapy was the most cost-effective strategy and had the lowest cost per QALY (US $462/QALY). The second most cost-effective option was tenofovir (US $495/QALY). The cost-effectiveness rates of both drugs were acceptable because the highest values (US $495/QALY) did not exceed the threshold of acceptability, which is up to three times the national gross domestic product (GDP) per capita (US $31,252.94/QALY) according to the recommendations of the World Health Organization [25].

The other drugs were associated with higher costs and lower effectiveness. The cost of peginterferon treatment considerably exceeded the threshold of acceptability.

These results were compared with the findings of other economic models, although our findings are not in agreement with those obtained by Colombo et al. (2011) and Buti et al. (2009) [26,27], which suggested that tenofovir was the most cost-effective option. This discrepancy may be due to the variability in the cost of lamivudine. In Europe, the cost of this drug is 24 times higher than that in Brazil. In a study of chronic HBeAg-positive patients by Almeida et al.[28], as requested by the SUS, interferon was the most cost-effective option. Methodological differences may account for these contrasting results. In the model by Almeida et al.[28], the time horizon was 40 years, the measures of effectiveness were taken from the literature and 6 states of health were used to model disease progression. In our model, the time horizon was 30 years, the utility measures were based on the consensus of experts and 12 states of health were used to model disease progression.

Sensitivity Analysis

In the sensitivity analysis, the variations in the discount rates affected the results regarding treatment costs and effectiveness; however, these variations did not affect the results regarding the most cost-effective strategies and the dominated strategies.

In the analysis, the variations in the total cost of the treatments were applied only to lamivudine, tenofovir and entecavir. The other drugs were not included in the analysis due to their high cost and low effectiveness.

The cost of lamivudine ranged from US $265.44 to US $967.20. The first value is the lower purchase price of the drug according to the SUS (US $0.38/tablet), whereas the second value is the higher unit price that is typically found in Brazil (US $1.32/tablet) [15]. The variations in the price of lamivudine did not affect the result of it being the most cost-effective option. Table 6 shows the values that were obtained in the analysis.

Variations in the cost of tenofovir and entecavir were separately calculated for each drug. Due to the lack of information about the different price ranges for these drugs, a value of 20% above and below the estimated cost was established. The variations did not affect the results that were obtained using the model.

Regarding the sensitivity of the model to the variations in the probabilities of response to follow-up therapy (pRef) with lamivudine, an analysis was performed in which the response was reduced by 5 to 20% ranges, where the best response obtained was

the initial reference. Lamivudine was predominant over all of the drugs until there was a 40% reduction in the probability of a response. From this point on, the use of tenofovir became the most cost-effective option. This information is particularly relevant because studies have demonstrated a pRef of 19% for lamivudine [29].

Table 6: Analysis of the sensitivity to the total cost of treatment with lamivudine.

C_med	Strategy	Cost* (US$)	Incremental Cost (US$)	Effect (QALY)	Incremental Effect (QALY)	C/E (US$/QALY)	ICER - US$/QALY
265.44*	Lamivudine	5,606.45	0	12.124		462	
	Tenofovir	6,031.91	425.46	12.192	0.068	494.61	6,293
	Entecavir	7,023.44		12.192		575.98	(Dominated)
651.41*	Lamivudine	5,795.65	0	12.124		478	
	Tenofovir	6,031.91	236.26	12.192	0.068	494.61	3,495
	Entecavir	7,023.44		12.192		575.98	(Dominated)
967.20	Lamivudine	5,950.45	0	12.124		490.69	
	Tenofovir	6,031.91	81.46	12.192	0.068	494.61	1,205
	Entecavir	7,023.44		12.192		575.98	(Dominated)

Source: Developed by the authors; C_med: total cost of treatment; *ICER=Incremental cost-effectiveness ratio.

*Relative to the unit price of US $0.39; *Relative to the unit price of US $0.95.

Regarding tenofovir, which was the second most cost-effective option, the sensitivity analysis of the pRef changes was performed using data that were estimates based on information from studies of other drugs. The analysis had an estimated pRef of 77% as the initial reference [30]. The test demonstrated that when the pRef for tenofovir was reduced to values lower than 71%, entecavir became the second most cost-effective strategy and the only strategy that was not dominated.

The pRef of tenofovir ranged from 0.715 to 0.765, which suggested that entecavir was the third most cost-effective strategy. When the pRef of tenofovir reached 0.77, entecavir became a dominated strategy.

The sensitivity analyses, which included the discount rates, the probability of response at the end of treatment and the total cost of pharmacotherapy, confirmed that lamivudine was the most cost-effective strategy. If the unit value of lamivudine was ≥ US $1.32, the results would favour tenofovir.

The limitations of this study included a lack of data on the viral resistance profiles for the drugs that were tested, a lack of precision in the assessment of utilities and patient profiles, the exclusion of adverse effects and the inclusion of estimates that were obtained from the literature.

Viral resistance information for several drugs was incomplete; therefore, this information could not be used in the model but could have affected the results. High rates of viral resistance to lamivudine require the adoption of a rescue therapy, which would increase the cost of treatment and reduce the cost-effectiveness. Regarding the measure of utility that was applied in the model, the imprecision in the assessment of the utilities, which was derived from a panel of experts, should be emphasized.

The patient profile in this study does not allow for the extrapolation of the results to other population profiles. However, this group was selected because of the greater prevalence and clinical relevance of these patients with chronic HBV infection.

Because the model did not consider the possible adverse effects of the drugs in the protocol, their costs were not included in the assessment.

Finally, the sources of data that supported the model were international studies of Asian populations, which may not reflect the responses in the Brazilian population.

CONCLUSIONS

Approximately 360 million people around the world are chronic carriers of HBV. In the proposed model, the most cost-effective therapeutic option was lamivudine. Other Markov chain models of the natural history of chronic hepatitis B in HBeAg-positive and -negative patients indicated that tenofovir was the most cost-effective therapeutic strategy. However, the current cost of lamivudine affects this finding. Lamivudine is the most cost-effective strategy for treating HBeAg-positive patients when the price threshold of US $23,529, and the high rates of viral resistance to lamivudine treatment are considered. In HBeAg-negative individuals, this assumption is not subject to any conditions.

Considering the lack of mathematical models that analyse treatment responses at the end of follow-up in HBeAg-positive and -negative individuals and the lack of conclusive data on the efficacy of several drugs that are used to treat chronic hepatitis B, more clinical studies and economic analyses are needed.

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REFERENCES

1. Lopes, CLR, Martins, RMB, Teles, SA, et al. Perfil soroepidemiológico da infecção pelo vírus da hepatite B em profissionais das unidades de hemodiálise de Goiânia-Goiás, Brasil Central. [Seroepidemiological profile of infection with hepatitis B virus in professionals from the haemodialysis units in Goiânia, Goiás, Central Brazil]. Rev. bras. educ. méd 2001; 34(6): 543-548.
2. World Health Organization (WHO). Weekly epidemiological Record Relevé épidémiologique hebdomadaire 2009; 40 (84): 405–420,. Available from: http://www.who.int/wer
3. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de DST, Aids e Hepatites Virais. Programa Nacional para a Prevenção e o Controle das Hepatites Virais [Brazil. Ministry of Health. Health Surveillance Secretary. Department of STI, AIDS and Viral Hepatitis. National Program for the Prevention and Control of Viral Hepatitis]. Protocolo Clinico e Diretrizes Terapêuticas para o Tratamento da Hepatite Viral Crônica B e Coinfeccoes [Clinical Protocol and Therapeutic Guidelines for the Treatment of Chronic Viral Hepatitis B and Co-infections]. Brasilia – DF, 2011: 128.
4. Verdugo RM, Berenguer MA, Navarro MVG et al. Tratamiento farmacológico de la hepatitis B. [Pharmacological treatment of hepatitis B] Farm Hospital 2008; 4 (32):234-248.
5. Fonseca JCF. História natural da hepatite crônica B. [Natural history of chronic hepatitis B] Rev Soc Bras Med Trop 2007; 40 (6):.672-677.
6. Iloeje UH, Yang HI, Jen CL, J Su, Wang LY et al. Risk and Predictors of Mortality Associated With Chronic Hepatitis B Infection. Clin Gastroenterol Hepatol 2007; 5 (8):921-931.

7. Ferreira MS. Diagnóstico e tratamento da hepatite B. [Diagnosis and treatment of hepatitis B] Rev Soc Bras Med Trop 2000; 33 (4):389-400.
8. Hsu YS, Chien RN, Yeh CT, Sheen I, Chiou HY et al. Long-Term Outcome After Spontaneous HBeAg Seroconversion in Patients With Chronic Hepatitis B. Hepatology 2002; 35(6):1522-1527.
9. Ferreira CT; da Silveira TR. Hepatites virais: aspectos da epidemiologia e da prevenção. [Viral hepatitis: aspects of epidemiology and prevention] Rev. Bras. Epidemiologia 2004; 7 (4): 473-487.
10. Keeffe EB, Dieterich DT, Han SHB, Jacobson IM et al. A Treatment Algorithm for the Management of Chronic Hepatitis B Virus Infection in the United States: An Update. Clin Gastroenterol Hepatol 2006; 4 (8) :936-962.
11. Alberti A, Clumeck N, Collins S, Gerlich W et al. Short Statement of the first European consensus conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. J Hepatol 2005; 42(5):615-624.
12. DATA, version 1.0.3, 2009, Tree Age Software, Inc., Williamstown, MA.
13. Kanwal F, Gralnek IM, Martin P, Dulai GS, Farid M, Spiegel BM et al. Treatment Alternatives for Chronic Hepatitis B Virus Infection: A Cost-Effectiveness Analysis. Ann Inter Med 2005; 142 (10):.821-w196,.
14. Dhumeaux D, Marcellin P; Le Rebours E. Treatment of hepatitis C. The 2002 French Consensus. Gut 2003; 52 (12): 1784-1787.
15. Compras Net - Portal de compras do Governo Federal. [COMPRAS NET- Shopping portal of the Federal Government] Available from: <http://www.comprasnet.gov.br/>.
16. Marcellin P, Chang TT, Lim SG, Tong MJ et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med. 2003; 348(9):808-16
17. Marcellin P, Heathcote EJ, Buti M, Gane E et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med. 2008; 359(23):2442-55
18. Chang TT, Gish RG, de Man R, Gadano A et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med. 2006; 354(10):1001-10.
19. Liu CJ, Lai MY, Chao YC, Liao LY et al. Interferon alpha-2b with and without ribavirin in the treatment of hepatitis B and antigen-positive chronic hepatitis B: a randomized study. Hepatology 2006; 43(4):742-9.
20. Lai CL, Shouval D, Lok AS, Chang TT et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med. 2006; 354(10):1011-20.
21. Janssen HL, van Zonneveld M, Senturk H, Zeuzem S et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. Lancet 2005; 365(9454):123-9.
22. Schalm S, Heathcote J, Cianciara J, Farrell G et al. Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomised trial. Gut, 2000; 46(4): 562–568.
23. Cooksley WG, Piratvisuth T, Lee SD, Mahachai V et al. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. J Viral Hepat. 2003; 10(4):298-305.
24. Woo G, Tomlinson G, Nishikawa Y, Kowgier M et al. Tenofovir and Entecavir are the most effective antiviral agents for chronic hepatitis B: A Systematic Review and Bayesian Meta-analyses. Gastroenterology 2010; 139 (4): 1218-1229.
25. World Health Organization (WHO). Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis. Cost-effectiveness thresholds. Available from: http://www.who.int/choice/costs/CER_thresholds/en/index.html.
26. Colombo GL, Gaeta GB, Viganò M, Di Matteo S. A cost-effectiveness analysis of different therapies in patients with chronic hepatitis B in Italy. Clinicoecon Outcomes Res. 2011; 3: 37-46.
27. Buti M, Brosa M, Casado MA, Rueda M. Modeling the cost-effectiveness of different oral antiviral therapies in patients with chronic hepatitis B. J Hepatol 2009; 51(4): 640-646.
28. Almeida MA, Silva AL, Cherchiglia ML, Andrade EIG et al. Chronic Hepatitis B Treatment: The Cost-Effectiveness of Interferon Compared to Lamivudine. Value in Health 2011; 14: S24-S28.
29. Lau GKK, Piratvisuth T, Luo KX, Marcellin P, et al. Peginterferon Alfa-2a, Lamivudine, and the Combination for HBeAg-Positive Chronic Hepatitis B. N Engl J Med 2005; 352; 2686-2695.
30. Gish RG, Lok AS, Chang TT, de Man RA, Gadano A et al. Entecavir Therapy for up to 96 Weeks in Patients With HBeAg-Positive Chronic Hepatitis B. Gastroenterology 2007; 133(5):1437-1444.