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Review

Economics of chronic hepatitis B and hepatitis C☆

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Although not all patients develop progressive liver disease, chronic hepatitis B and chronic hepatitis C infections cause substantial morbidity and mortality worldwide. To address this need, many new antiviral treatments have become available over the past 10 years. While safety, efficacy, and therapeutic indications have been well established for these agents, the economics of antiviral treatment have become increasingly a focus of discussion for physicians, policymakers, and health payers. In this paper, we will elucidate some economic principles using examples from the treatment of hepatitis B and C. In particular, we will examine the considerations in estimating drug costs, methods for performing economic analyses and lastly summarize published cost-effectiveness analyses for antiviral treatments of chronic hepatitis B and chronic hepatitis C. This review should help clinicians understand economic issues regarding new drugs and answer questions about whether the clinical benefit provided by a medication justifies its expense.

***Keywords*: Chronic hepatitis B infection; Chronic hepatitis C infection; Treatment; Cost-effective analysis**

1. Introduction

An estimated 2 billion people worldwide had been infected with the hepatitis B virus (HBV) resulting in perhaps 400 million chronic infections in 2000 [1]. In the United States, the prevalence is 1.25 million [2,3], and in Asia it is 300 million [4]. Hepatitis C virus (HCV) infection affects 170 million people worldwide (4 million in the US and 5 million in Western Europe) [5,6]. Although the majority of those with chronic hepatitis B or C infection will not develop complications, 15–40% may develop cirrhosis, liver failure, or hepatocellular carcinoma (HCC) [3,7]. Thus, hepatitis B accounts for over 500,000 to 1 million deaths worldwide annually [2,8], and perhaps 65 million of those chronically infected may die from hepatitis B over their lifetime [1]. Similarly, 4–22% of patients with chronic hepatitis C may progress to cirrhosis after 20 years [7,9] with 280,000 deaths annually worldwide [10].

Although antiviral treatments can eradicate infection, selection of patients for treatment varies among physicians [11–13]. Consequently, hepatitis B and C have been major foci for international consensus conferences and societal guidelines [3,8,14–18], and with recent treatment advances [19], other groups have proposed additional treatment algorithms [19–21]. In particular because of uncertainty surrounding the likelihood of progression [22] and response to antiviral treatment, these statements help identify who should be treated with which treatments for how long and with monitoring of which serological outcomes. Increasingly, however, clinicians are being asked to consider the

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Abbreviations: CHB, chronic hepatitis B; HBV, hepatitis B virus; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

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economic consequences of their treatment choices [3,14]. This paper will examine economic principles involved in antiviral therapy for chronic hepatitis B and C, in particular, the costs of therapy, alternative methods for examining the economic implications of therapy, and lastly cost-effectiveness evaluations of hepatitis B and C treatments.

2. Costs of antiviral treatment

Currently, six antiviral treatments have been approved in various countries for the treatment of chronic hepatitis B: interferon alfa-2b, lamivudine, adefovir, entecavir, telbivudine, and peginterferon alfa-2a. Table 1 [11,23–27] lists their 2006 annual average wholesale costs in the United States. Over a year, interferon has a "high" cost and lamivudine has a "low" one with adefovir being "intermediate" [28]. Such a short-time horizon, however, ignores the likelihood that oral drugs may be taken lifelong [19], such as for HBeAg-negative chronic hepatitis B, so to put the 48 week cost of peginterferon in perspective, 6.4 years of lamivudine, 2.6 years of adefovir and 2.1 years of entecavir have equivalent costs. This illustrates the importance of the analytic time horizon during which the economics of treatment are considered.

3. Clinical benefit in economic assessment

Whether a drug provides sufficient clinical benefit to justify its cost involves determining the drug's effectiveness to assess its "value." For hepatitis B, one measure of benefit would be HBeAg seroconversion. Of course, in the absence of direct head-to-head trial comparisons, this assumes that the clinical populations were similar, but differences in patient characteristics resulting from alternative inclusion or exclusion criteria or patient recruitment sites (resulting in different proportions of Asian patients or genotypes for example) may confound such cross-trial comparisons [29,30]. For the purposes of illustration, Table 1 [11,23–27] assumes that such a comparative efficacy assessment is valid. Dividing the 1-year drug cost by its 1-year seroconversion rate [11,24,27] yields the average cost per seroconversion. An alternative measure of clinical benefit, however, changes the average cost per clinical benefit, e.g., undetectable PCR (Table 1), lowering the average cost per outcome for the oral medications but raising it for peginterferon.

When changing the time horizon to 2 years, seroconversion rates increase but also costs (Table 1). The above average cost analyses simply divide the 2-year costs by the 2-year response, but another approach called incremental cost-effectiveness analysis considers only the additional cost of a second year of treatment and only the additional seroconversion rate during the second year (the difference in seroconversion rate between the first and second year). In more general terms, the incremental cost effectiveness ratio (ICER) is given by the following:

$$\frac{\text{Cost with New Intervention} - \text{Cost with Standard Care}}{\text{Effectiveness with New Intervention} - \text{Effectiveness with Standard Care}}$$

where for this example the new intervention is a second year of treatment and standard care is 1 year.

In such calculations, the difference in cost and the difference in effectiveness may either be positive or negative resulting in four alternative outcomes where the new intervention compared to standard care: (1) is "dominated" or inferior, resulting in higher costs and lower effectiveness (positive incremental costs and negative incremental effectiveness); (2) is "cost-saving," resulting in lower costs and higher effectiveness (negative incremental costs and positive incremental effectiveness); (3) results in lower costs and lower effectiveness (negative incremental costs and negative incremental effectiveness); or (4) results in higher costs and higher effectiveness (positive incremental costs and positive incremental effectiveness). For the latter two possibilities, an ICER is calculated to determine the additional cost to obtain one unit of effectiveness or benefit. "Cost-effectiveness" does not, however, reduce costs

Table 1
Costs and 1-year and 2-year seroconversion and undetectable HBV DNA rates for chronic hepatitis B [11,23–27]

Treatment	1-year Wholesale price (AWP)	1-year HBeAg seroconversion rate (%)	Average cost per 1-year HBeAg seroconversion	1-year Undetectable HBV DNA rate (%)	Average cost per 1-year undetectable HBV DNA	2-year HBeAg seroconversion rate (%)	Average cost per 2nd year HBeAg seroconversion	ICER[a] per additional 2nd year HBeAg seroconversion
Lamivudine	$2888	17	$17,000	44	$6600	25	$23,100	$36,100
Adefovir	$7245	12	$60,400	21	$34,500	29	$50,000	$42,600
Entecavir	$8643	21	$41,200	67	$12,900	31[b]	$55,800	$86,400
Peginterferon alfa-2a	$18,480	32	$57,800	25	$73,900			

This table shows the costs of the various antiviral treatments for chronic hepatitis B. It starts with the costs for 1 year, followed by the average cost per seroconversion for the first and second years and undetectable HBV DNA for the first year, and finishes with the incremental cost per additional second year seroconversion. This demonstrates the importance of outcome measures, time horizon, and average versus incremental cost-effectiveness.

[a] ICER, incremental cost-effectiveness ratio.

[b] Not all patients completed 2 years of treatment.