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Cost efficacy and cost–benefit of treatment of hepatitis C

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The combination of the high costs of new drugs and limited resources necessitates economic evaluation of all new therapeutic options. Socioeconomic evaluations seek to optimize the use of available resources by identifying, evaluating, measuring, and comparing various alternatives to interventions, diagnoses, or therapies. Thus, new interventions do not have to cost less if resources are used in a more efficient way.[1] The benefits of interventions are defined in terms of clinical, psychosocial or economic outcomes.

There are several types of economic evaluations. Those accepted as type 1 evidence include full economical evaluations in which multiple sensitivity analyses are conducted. Systematic reviews are considered to be type 1a evidence.[2] Full economical evaluations may be classified according to outcomes as cost reduction, profit–cost, cost-usefulness, cost-effectiveness and cost-benefit studies. In cost-reduction evaluations, alternatives that have similar outcomes are compared to identify the one with the lowest cost. In the other types of evaluations, interventions with different outcomes are compared in terms of morbidity and mortality (cost effectiveness), usefulness or quality of life (cost usefulness) or monetary units (cost–benefit).[3]

Impact of infection by hepatitis C virus

Assessment of the impact of a disease should be based on the effects of several factors such as:

1. longevity (mortality and years lost because of premature death),
2. morbidity (diminution of health and quality of life and increased need for medical assistance),
3. direct and indirect expenses of medical assistance, and
4. monetary losses related to income forfeited because of work disability or premature death.[4,5]

All parameters used to assess the impact of a disease should be expressed in terms of regional statistics on its prevalence and incidence, and the mortality and morbidity associated with it. Unfortunately, reliable statistics on hepatitis C do not exist for most countries. In 1990, the World Bank and the World Health Organization carried out a study of the impact of diseases worldwide in order to establish health policies.[6] Even though this study only evaluated the impact of hepatic disease in general, some estimates of the impact of chronic viral hepatitis were made. Of the 8.3 million people worldwide with liver cirrhosis in 1990, the condition was caused by chronic viral hepatitis C in 1.4 million cases; 10% of those with cirrhosis died that year. Of the 858,000 cases of hepatocarcinoma, 170,000 cases are estimated to be secondary to hepatitis C virus (HCV) infection; 100,000 died from hepatocarcinoma that year.[6,7] The corresponding years adjusted for disability (DALYs) could be as high as 4.2 million of DALYs.[7]

The United States of America has reliable statistics on HCV infection. In the National Health Survey[8] carried out between 1988 and 1994 with a sample population of 21,000 persons, 1.8% of people had anti-HCV antibodies, 74% of whom were positive for HCV RNA, i.e., they had active infections.[4] Extrapolation of these statistics to the population of the USA indicates that 3.1–4.8 million people have been in contact with the HCV, and about 2.7 million have active infections (95% CI = 2.4–3.0 million). The prevalence of HCV infection is greatest is among 30–49 year olds, which suggests that they contracted the infections 10 to 30 years ago. The major limitation of the survey is that it did not include groups of people such as the homeless, prisoners, orphans, and people in hospices, among whom the prevalence of HCV infection is as high as 40%–54%. Therefore, this study may underestimate the impact of the disease. Estimates of the incidence of HCV infection that are based on the data of the National System of Notifiable Diseases may also underestimate the incidence of hepatitis C, because acute and chronic hepatitis C is asymptomatic in a large percentage of subjects, many high-risk individuals do not have access to health systems, and health workers may under-record cases of hepatitis C.

The Centers for Disease Control in the USA used a catalytic model to predict that the incidence of hepatitis C would diminish progressively until an incidence of 1% was attained in 2003.[9] Even though the incidence of

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new cases of hepatitis C may diminish, the number of patients with cirrhosis and end-stage liver disease is expected to increase because chronic hepatitis C may take more than a decade to progress to an advanced stage. The Centers for Disease Control estimate that a fourfold increase in the number of subjects with advanced liver disease will occur between 1990 and 2015. Davis et al. used a previously validated natural history model to estimate that by 2040, liver cirrhosis related to HCV will have increased by 38%, decompensated liver cirrhosis will have increased by 124%, and hepatocarcinoma will have increased by more than 100%.[10]

Estimates of the mortality rates of hepatitis C patients are reliable because data on mortalities from 1990 to 1998 included deaths from end-stage liver disease, viral hepatitis, or sequels related to liver disease.[10] The most recent report ranked chronic liver disease as the tenth most frequent cause of death in the United States from 1990 to 1998 and revealed that mortality related to HCV increased by 220% between 1993 and 1998. The number and proportion of patients awaiting liver transplants increased progressively over the past 10 years. In addition, the number of hospitalizations of patients with an 1CV-positive condition has increased; in 1998, 2% (140,000) of all hospital releases were HCV positive. Hospital expenses associated with treatment of hepatitis C patients in the United States exceed 1,000 million dollars.[4,5] A study by the American Gastroenterology Association estimated that 317,000 consultations costing 24 million dollars were related to the treatment of hepatitis C during 1998, and that 530 million dollars was spent on antiviral treatment of HCV.[11] Other authors showed that hospitalization, medical visits, and the use of other health resources by HCV-infected patients increased by 25%–30% per year between 1994 and 2001.[12]

The trend in the United States is similar to that in other countries. Deuffic et al. estimated that mortality caused by HCV-induced hepatocarcinoma will increase by 150% in men and by 200% in women by 2020.[13] In another model prepared for the Australian population, Law estimated that the number of cases of HCV-related liver cirrhosis will increase by 102% by 2010 and that of HCV-related hepatocarcinoma will increase by 150%.[14] Recently, Buti et al.[15] estimated that despite an anticipated reduction in the number of new cases of HCV infection, the proportion of hepatitis C patients with cirrhosis will increase to 14% and morbidity will increase to 10% by 2030. There are few publications about the costs of HCV infection in Latin America. A multicenter study carried out at third-level service hospitals in Mexico established that chronic HCV infection is the second most frequent cause of liver cirrhosis.[16] Another study suggested that the prevalence of patients with HCV-induced liver cirrhosis would increase by more than 70%.[17]

Cost effectiveness of combined antiviral treatment with pegylated interferon and ribavirin

The objectives of treatment of chronic hepatitis C are to eliminate the virus and halt the progress of liver damage. A sustained viral response (SVR) is associated with improved hepatic function, liver histology, quality of life, and survival. The latter effect, as well as the possible modulator role of antiviral treatment on liver fibrogenesis is found in a prospective evaluation.

Treatment of chronic HCV infection is based on a combination of interferon and ribavirin. Large multicenter studies[18,19] have shown that approximately 40% of patients who are treated with this combination of drugs for 48 weeks will attain an SVR, defined as undetectable viral RNA 6 months after termination of treatment.

Recently, pegylated interferon was approved for use in patients with chronic HCV liver disease. The binding of polyethylene glycol to interferon improves its pharmacokinetics, allowing it to be administered once weekly. The combination of pegylated interferon and ribavirin results in an SVR of 50%, which is especially important for patients with HCV genotype 1.[20-22] Other studies showed that patients with HCV genotypes 2 and 3 may be treated with lower doses of ribavirin for shorter periods.[23]

Based on available information, the consensus of the National Institutes of Health of the United States[24] recommended that antiviral therapy for hepatitis C should be appropriate to the HCV genotype. Pegylated interferon alfa and 1000–1200 mg/day ribavirin for 48 weeks are recommended for genotype 1 and pegylated interferon alfa and 800 mg/d ribavirin for 24 weeks are recommended for genotypes 2 and 3.[24] This new combination of drugs has increased the cost of therapy.

The combination of interferon alfa and ribavirin is cost effective compared with other routine medical interventions.[25,28] Because combined antiviral therapy with pegylated interferon plus ribavirin is the treatment of choice for patients with chronic HCV, many evaluations have been conducted in various parts of the world, including England, Spain, Germany, and the USA. These studies, all of which constitute type 1 evidence, used models adapted to their respective countries to show that the combination of pegylated interferon and ribavirin is cost effective.[29–32]

Because systematic reviews are considered type 1a evidence, aspects of the two most recent systematic reviews are worthy of mention. The clinical efficacy and cost-effectiveness of treatment with pegylated interferon alfa 2a and with pegylated interferon alfa 2b plus ribavirin was evaluated at the request of the Health Technology Evaluation Program of the United Kingdom. Two randomized, controlled studies that compared pegylated interferon plus ribavirin with nonpegylated interferon plus ribavirin were analyzed, and four studies in which pegylated interferon monotherapy was compared with nonpe-

gylated interferon monotherapy were analyzed. The primary outcome of all studies was an SVR. A model of cost effectiveness was applied to a hypothetical cohort of 1,000 chronic hepatitis C patients over a period of 30 years. The relative risk of remaining infected after pegylated interferon plus ribavirin treatment was 17% lower than after unpegylated interferon plus ribavirin treatment. Patients with HCV genotypes 2 and 3 had the highest SVR and those infected with HCV genotype 1 had the lowest SVR. The relative risk of remaining infected after monotherapy with pegylated interferon was 20% less than after monotherapy with unpegylated interferon. Responses to monotherapy varied according to genotype and viral load. There were no significant differences between therapeutic regimens in the frequency or intensity of adverse effects. When compared to the cost of no treatment, the increasing cost per year of life adjusted for quality (AVAC) of treatment with pegylated interferon plus ribavirin for 48 weeks was £6045. Compared with the combination of nonpegylated interferon plus ribavirin, the increasing cost per AVAC of pegylated interferon plus ribavirin was £12,123. The increasing costs per AVAC were more favorable in patients with HCV genotypes 2 and 3 with low viral loads than those who received no treatment. Sensitivity analysis proved that the model was robust. All estimates were less than £30,000 per AVAC, which is the limit for cost effectiveness in the United Kingdom *(Table I)*. This study concluded that pegylated interferon in monotherapy and in combination with ribavirin achieves a higher SVR than nonpegylated interferon and is cost effective.[33]

The other study was performed by Siebert and Sroczynsky as part of the German team for hepatitis C model (GEHMO), as commissioner of Federal Germany Health and Social Security Ministery. This systematic review of published evidence was undertaken to determine the efficacy and cost-effectiveness of antiviral treatment with interferon or pegylated interferon combined with ribavirin in treatment-naïve patients chronically infected with HCV. A series of meta-analyses was made, and evidence tables were constructed. The Markov model of hepatitis C was applied to determine the long-term clinical efficacy, costs, and cost effectiveness of the therapeutic strategies. The model parameters were derived from German databases consisting of nine controlled randomized studies, two health technology evaluations, a Cochrane review, two meta-analyses, and seven economic evaluations. The meta-analysis showed that the proportion of nonresponders was reduced by 17% by the combination of pegylated interferon and ribavirin, which had an adjusted increasing cost of •9,800 per AVAC. This suggests that in treatment-naïve, chronic hepatitis C virus carriers, the combination of pegylated interferon and ribavirin is the most efficient and cost-effective treatment *(Table II)* and that it increases survival and improves quality of life.[34]

Analysis of data from studies of various types of pegylated interferon[21,22] revealed that it is possible to identify subjects who do not respond to therapy from their viral response at twelve weeks of combined antiviral treatment with a negative predictive value of 98%–100%. This finding enabled formulation of a treatment discontinuation rule for HCV genotype 1 patients who do not achieve early viral response, which is defined as

Table I. Subanalysis by genotype of increasing cost-usefulness discounted for the cost per year of life adjusted for quality (AVAC) for combined antiviral treatments in a model of 1,000 patients.

	AVAC*	AVACs gained	Net costs per AVAC gained
Genotype 1[a]			
Interferon + ribavirin**	22,743	–	–
Pegylated interferon + ribavirin***	23,098	355	£10,848
Genotypes 2 and 3[a]			
Interferon + ribavirin	23,631	–	–
Pegylated interferon + ribavirin	24,163	533	£7051
Genotypes 4, 5 and 6[b]			
Interferon + ribavirin	22,814	–	–
Pegylated interferon + ribavirin	23,240	426	£8946

*AVAC: year of life adjusted for quality
** Nonpegylated interferon and ribavirin for 48 weeks
*** Pegylated interferon and ribavirin for 48 weeks
[a] Based on the SVR reported by Fried et al.(22)
[b] Based on SVR reported by Manns et al.(21)

Table II. Increasing relationship cost effectiveness and relation incremental cost with an annual discount rate of 3% for various management strategies in patients with chronic hepatitis C.

	No treatment	Interferon *vs* no treatment	Interferon + ribavirin *vs* interferon	Pegylated interferon + ribavirin *vs* interferon
Life expectancy (years)	17.97	18.45	19.19	19.90
Increasing life expectancy (years)	–	0.48	0.73	1.45
Relation increasing cost effectiveness (£/year)	–	5,800	12,300	10,300
Years of life adjusted for quality (AVACs)	16.07	16.60	17.38	18.13
Incremental AVACs	–	0.53	0.78	1.53
Relation increasing cost usefulness (£/AVAC)	–	5300	11,600	9800

Adapted from: Siebert et al., Int J Technol Assess Health Care. 2005;21(1):55–65.

a reduction to a viral load equal to or greater than 2 logarithms with respect to the baseline load at week 12. This rule does not apply to patients with HCV genotypes 2 and 3 because 90%–99% of them will achieve an SVR, rendering this criterion not cost effective. Modeling to estimate cost reductions and resource optimization shows that this strategy is highly cost-effective (40%–44% reduction of in lasting and 15.7%–45% reduction in treatment costs).[33,35–36] Because of the low probability of achieving SVR (0%–2%) to keep therapy on those patients not achieving early viral response, conditioning a non-cost-effective ratio in the different models studied.[33,35,36]

The availability of a safe, efficient and cost-effective antiviral therapy invokes the question of what would happen if all subjects that are infected with HCV at present were offered treatment. Models indicate that treatment of 10% or 50% of the HCV-infected population with pegylated interferon plus ribavirin would reduce morbidity by 6% and 26% and mortality by 4% and 20%, respectively.[10,15]

The following require further investigation: comparison between both types of pegylated interferon, retreatment of patients who have not responded to therapy previously, long-term maintenance treatment, treatment efficacy and evolution in long-term patients who present with comorbidities, prospective validation, adjustment of rules for establishing treatment regimens, determination of short-term regimen efficacy in patients who are easy to treat (genotype 2, low viral load), and determination of long-term regimens in subjects with less favorable predictive factors. However, as the progression of the disease differs between patients, detailed evaluation of the eligibility of patients and antiviral management must be done on an individual basis.

Recommendations of the consensus panel:

From a theoretical point of view, is it advisable to treat all patients with HCV infection?

Consensus was not reached. However, the majority of panel members (56%) recommended treating all patients with chronic HCV infection. Models indicate that treatment of 10% or 50% of the HCV-infected population with pegylated interferon plus ribavirin would reduce morbidity by 6% and 26% and mortality by 4% and 20%, respectively, with evidence quality type 1 (l-m).

Evidence quality: 1

Is there a cost-benefit to discontinuation of treatment according to viral responses at week 12?

The panel of the consensus recommends application of the discontinuation rule for viral loads greater than or equal to two logarithms from baseline at week 12.

Evidence quality: 1

At present, is it justifiable to offer treatment to patients with compensated liver cirrhosis?

The panel considers treatment of subjects with compensated liver cirrhosis justifiable in terms of cost benefit.

Evidence quality: 1

Do you consider the use of conventional interferon alfa and ribavirin for patients with HCV genotypes 2 and 3a to be a resource-saving strategy?

Most of the panel (55%) considered the use of regular interferon in combination with ribavirin for patients with HCV genotypes 2 and 3 unacceptable as a resource-saving strategy.

Evidence quality: 1

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