Motion – The available treatments for hepatitis C are cost effective: Arguments for the motion

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The treatment of hepatitis C has evolved over the past decade, and a combination of interferon (IFN), pegylated or standard type, and ribavirin is now acknowledged as the therapy of choice. Questions remain, however, about the duration of treatment and which patients are the most likely to benefit from therapy. Cost effectiveness analyses (CEAs) have been employed to answer these questions. Before the results can be interpreted appropriately, however, clinicians must make themselves aware of the underlying assumptions and the nature of the 'reference' case. Moreover, certain parameters, including quality-of-life evaluations, may not be easily translated from one jurisdiction to another. The costs and benefits of treatment are often very sensitive to such factors as patient age, viral load, histological severity and the viral genotype. Randomized controlled clinical trials, and the CEAs on which they are based, have shown that combination therapy is more cost effective than IFN monotherapy, and that both are cost effective compared with no treatment. Ongoing research on the use of pegylated IFN, weight-adjusted dosing of ribavirin, and the treatment of relapsers and nonresponders will provide valuable data that could be incorporated into future CEAs. Health care resources are vast, but not limitless. Therefore, health care providers need to become aware of how best to allocate resources to the general population. CEAs can facilitate this process by determining which treatment strategies are likely to yield the greatest clinical benefits without excessive expenditures.

Key Words: *Cost effectiveness; Hepatitis C; Treatment*

Motion - Les traitements disponibles contre l'hépatite C sont rentables : Arguments en faveur de la motion

RÉSUMÉ : Le traitement de l'hépatite C a évolué depuis dix ans, et une combinaison d'interféron (ITF), PEG ou standard, et de ribavirine est maintenant reconnue comme traitement de choix. Toutefois, des questions demeurent sur la durée du traitement et sur les patients les plus susceptibles de profiter du traitement. Des analyses coût-efficacité (ACE) ont été utilisées pour répondre à ces questions. Cependant, avant de pouvoir interpréter les résultats de manière convenable, les cliniciens doivent se sensibiliser aux hypothèses sous-jacentes et à la nature du cas de « référence ». De plus, certains paramètres, y compris les évaluations de la qualité de vie, ne se traduisent pas toujours facilement d'un territoire à l'autre. Les coûts et les avantages du traitement sont souvent très sensibles à des facteurs comme l'âge du patient, la charge virale, la gravité histologique et le génotype viral. Des essais cliniques aléatoires et contrôlés et les ACE sur lesquelles ils se fondent démontrent que le traitement combiné est plus rentable que la monothérapie à l'ITF, et que tous deux sont rentables par rapport à l'absence de traitement. Des recherches qui se poursuivent sur le PEG-interféron, la dose de ribavirine rajustée selon le poids et le traitement des récidives et des personnes qui n'ont pas réagi, fourniront des données précieuses qui pourront être incluses dans de futures ACE. Les ressources de santé sont vastes, mais pas illimitées. Par conséquent, les dispensateurs de soins doivent être sensibilisés à la meilleure manière de distribuer les ressources à la population générale. Les ACE peuvent faciliter ce processus en permettant d'établir les stratégies de traitement susceptibles de procurer les meilleurs bénéfices cliniques sans s'accompagner de dépenses excessives.

KEY ASPECTS OF COST EFFECTIVENESS ANALYSES AS THEY RELATE TO HEPATITIS C TREATMENT

The perspective of cost effectiveness analyses

Most cost effectiveness analyses (CEAs) are undertaken from the perspective of society in general (ie, the public interest is served rather than that of any particular individual or group) (1). This is viewed as the most ethical approach, against which other perspectives can be judged. The societal perspective reconciles the health care needs of the population with the limitations to available resources, and is most able to determine the cost implications of competing health care strategies. On the other hand, such a perspective may not necessarily be readily usable by clinicians in the daily care of patients. Clinicians must determine whether the results of a CEA are valid and applicable to their own patients.

The 'reference' or 'base' case

The use of a 'reference case' is recommended, so that meaningful comparisons can be made among different CEAs (1). It should be representative of the target population for the intervention and provide details regarding the event pathway. Unfortunately, CEAs that address the treatment of hepatitis C virus (HCV) use different reference cases and, therefore, involve different patient populations.

The clinician cannot adequately interpret the results of a CEA without being aware of the target population. For example, because outcome measures, such as incremental cost effectiveness ratios (ICERs) and numbers of life-years gained, vary with the age of the target population, a CEA that involves 35-year-old patients (2) may not be comparable with one concerning patients who are 45 years old (3). Other parameters that can affect the results and that vary

among different CEAs include indications for stopping treatment, retreatment of relapsers and nonresponders, and assumptions about patient compliance (Table 1).

The event pathway provides details about the progression of the disease and the effects of the intervention. The complexity of event pathways is determined by the number of transitions, from one health state to another, that are included. For example, the model of health states used by Bennett et al (2) was more detailed and incorporated more transition states than that employed by Younossi et al (3).

Finally, data regarding monetary and resource expenditures, therapeutic effectiveness and utility weights (quality-of-life [QOL] measures) are assigned to each of the events in the disease pathway. The validity of the CEA ultimately depends on the source and accuracy of these data. In Table 2, the ideal data sources (inputs) are compared with sources that have been used in the published CEAs on HCV treatment.

The characteristics of the target population, QOL estimates and costs of the intervention vary by country and locale. Therefore, country- or even locale-specific data should ideally be used. The perspective used and the sources of information regarding resource, utility and cost inputs for three recently published studies (4-6) comparing interferon (IFN) with IFN plus ribavirin are summarized in Table 3. In none of the CEAs were the data sources entirely country-specific. Authors frequently cite data on therapeutic effectiveness from a variety of sources to increase the precision of the effectiveness estimates. For example, the Swedish study by Sagmeister et al (4) employed data from European, Canadian and American patient populations. It would be most appropriate to use country-specific sources of utility data, but this is not uniformly done; for example the QOL weights derived from an expert panel of American hepatol-

TABLE 1
Reference case and treatment-related assumptions used in cost effectiveness analyses on hepatitis C virus treatment (American studies only)

Authors (reference)	Reference case	Treatment-related assumptions made by the authors
Bennett et al (2)	35-year-old patient with mild histological disease	Relapsers were not retreated and prognosis was the same as that of nonresponders No histological benefits in virological nonresponders
Kim et al (8)	40-year-old patient with chronic hepatitis	Treatment was discontinued at 12 weeks if there was no biochemical response Relapsers and nonresponders have the same prognosis as untreated patients No histological benefits in virological nonresponders
Younossi et al (3)	45-year-old man with elevated alanine transferase and chronic hepatitis but without cirrhosis	Included the use of second-line therapies for relapsers and nonresponders No histological benefits in virological nonresponders
Wong et al (6)	Not stated	No histological benefits in virological nonresponders
	Target population the same as in clinical trial: mean aged 42 years, 66% male, 95% without cirrhosis	Treatment discontinued at 12 weeks (interferon [IFN]) or at 24 weeks (IFN plus ribavirin) in virological nonresponders
Sinha and Das (16)	10-year-old child with chronic hepatitis	Relapsers were not retreated and prognosis was the same as that for nonresponders Patients were 100% compliant There were no treatment-related complications

TABLE 2
Ideal data sources versus actual data sources for cost effectiveness analyses (CEAs) on hepatitis C virus (HCV) treatment

	Ideal data source	Actual data source in published CEAs
Effectiveness of antiviral therapy	Data from a large sample of HCV patients treated in clinical practices • Long-term benefits (decades after intervention) • Impact on rates of cirrhosis and hepatocellular carcinoma (which are the main sources of morbidity and mortality)	Sustained virological response rates from randomized controlled trials with six to 12 months of follow-up and limited data on histological improvement
Resource utilization and cost data	Provider costs Overhead/hospital/outpatient costs Time costs for wages in target population Health care costs related to lost or extended years of life	Third-party payments to providers to estimate provider costs Ratios of cost to charge to adjust hospital prices Management accounting systems to estimate hospital and outpatient costs American general population wages
Utility estimates	Data from representative population of HCV patients (treated and untreated) using health-stage classification system (eg, Health Utilities Index)	'Expert' panel of health care providers (hepatologists)

TABLE 3
Comparison of perspective and sources of information for inputs in cost effectiveness analyses on interferon and ribavirin

	Buti et al (5)	Wong et al (6)	Sagmeister et al (4)
Viewpoint of analysis	Payer (Spanish health authorities)	Societal	Societal
Source of effectiveness	Study by Poynard et al (11)	Studies by Poynard et al (11) and McHutchison et al (17)	Studies by Poynard et al (11) and McHutchison et al (17)
Source of quality-of-life weights	Expert panel of American hepatologists	Expert panel of American hepatologists	Panel of five Swiss physicians (time trade-off technique)
Estimates of resource use	Database of health care utilization in Spain (SOIKOS)	Product label for recommendations regarding follow-up plus American expert panel	Panel of five Swiss physicians
Sources of cost data	Database of health care cost elements in Spain	University of Florida hospital and physician costs (not charges) Wholesale costs of drugs Assumed no additional costs related to treatment complications	Database of the Swiss Hospital Association Reimbursement tariffs in Sweden Current retail prices of drugs

ogists (as used by Buti et al [5]) may not be appropriate for a Spanish patient population.

Reporting of results: what is the outcome of interest?
Several outcome measures are widely used in the literature:

• Quality-adjusted life-years (QALYs): This is regarded as the 'gold standard' for evaluating the effects of different health interventions.

• Life-years gained: This is often reported but, because it is not adjusted for the QOL, it distinguishes life-saving from quality-enhancing effects of the intervention.

• ICER: This is the cost per QALY gained by the intervention compared with either an alternative or

no intervention. An intervention is typically considered cost effective if it has an ICER of $50,000/QALY gained or less, although not all HCV studies have used this cut-off value. For example, Buti et al (5) decided that therapies with ICERs above €25,000/QALY gained were not cost effective.

Dealing with uncertainty
Variance in the estimates of disease prognosis, costs and resource utilization, and effectiveness of the intervention lead to uncertainties about its economic impact. The conventional method for dealing with these uncertainties is to undertake a sensitivity analysis, whereby the estimates of key components of the model are altered to assess their impact on the cost effectiveness ratios. The influence of demographic factors, such as age, sex or race, can also be investigated in this way.

CEAs OF ANTI-HCV THERAPY IN TREATMENT-NAIVE PATIENTS

Interferon versus no treatment

Two studies (2,7) compared a six-month course of IFN with no treatment. Dusheiko et al (7) considered a hypothetical cohort of HCV patients aged 25 to 35 years, and found that the ICERs ranged from £420 to £525 (approximately US$630 to US$790).

Bennett et al (2) considered patients with mild histological disease at the time of treatment. The discounted ICERs varied significantly with the age of the patient: $530 for 20-year-olds, $7,100 for 50-year-olds and $62,000 for 70-year-olds. Moreover, the results were affected by the cost of IFN treatment and the rates of transition from mild to moderate disease and from moderate chronic hepatitis to cirrhosis.

IFN for six versus 12 months

Kim et al (8) compared six versus 12 months of IFN treatment and found that both were cost effective ($4,000 and $5,000/QALY gained, respectively) and comparable with other medical interventions. Even though 12 months of IFN was more efficacious (resulted in more QALYs and fewer deaths), six months of treatment was more cost effective (consumed fewer dollars per QALY gained). Age had a significant effect, in that 50-year-old patients with 'worst case scenario' factors had marginal cost effectiveness ratios exceeding $50,000/QALY gained. The cost and effectiveness of IFN therapy, the cost of treatment for decompensated cirrhosis, the QOL of patients with chronic hepatitis C, and the rate of disease progression all significantly influenced the results.

IFN versus IFN plus ribavirin

Six CEAs have compared these two treatment strategies (3-6,9,10).

Younossi et al (3) compared IFN monotherapy in four different combination treatment strategies:

- 12 months of combination therapy;
- IFN followed by combination therapy for relapsers;
- IFN followed by combination therapy for relapsers or nonresponders;
- Combination therapy with the duration based on HCV genotype (48 weeks for genotype 1 and 24 weeks for other genotypes).

The fourth strategy was both the most effective and the most cost effective, with a discounted ICER of $7,500/QALY gained. Sensitivity analyses, involving the cost of combination therapy and the response and relapse rates, confirmed that the results were generally robust. However, the cost effectiveness ratios were sensitive to the effects of age and the effectiveness of combination therapy. The cost effectiveness ratio increased to greater than $50,000/QALY gained if end-of-treatment responses decreased to less than 30%.

Buti et al (5) compared combination IFN therapy for 48 weeks versus combination therapy for 24 weeks, and found that it was associated with ICERs of €8515 and €15,891 per QALY gained, respectively. They found that the ICER for 48 weeks of combination therapy, compared with 48 weeks of IFN, was markedly affected by the presence of unfavourable treatment characteristics. For example, the ICER was €45 per QALY gained for young (under age 50 years) female patients with mild histological changes, low viral load and viral genotype 2 or 3, but increased to €52,169 per QALY gained for older male patients with more severe disease, high viral load and genotype 1.

Wong et al (6) compared combination therapy for 24 or 48 weeks with 24 and 48 weeks of IFN alone. They found that combination therapy had ICERs of $5,400 and $7,700 per discounted QALY gained, respectively, compared with 48 weeks of IFN monotherapy. Combination therapy for 24 weeks was cost saving compared with 48 weeks of IFN monotherapy for patients with HCV genotype 2 or 3. Sensitivity analyses involving sex, initial histology, viral load, the presence of genotype 1 and number of favourable response characteristics caused the ICER for 24 weeks of combination therapy to vary from $250 to $11,600/QALY gained compared with 48 weeks of IFN monotherapy. Similar sensitivity analyses showed that, compared with 24 weeks of therapy, 48 weeks of combination therapy had ICERs of $2,500 to $50,200/QALY gained. The longer duration therapy was inferior, however, for patients with genotype 2 or 3 and for those with four or five favourable response characteristics.

Sagmeister et al (4) compared 24- and 48-week courses of combination therapy with 48 weeks of IFN monotherapy. Their results were similar to those of other investigators (5,6). For patients with HCV genotype non-1, 24 weeks of combination therapy was the most cost effective. For patients with genotype 1, 48 weeks of combination therapy prolonged life expectancy for those who responded by 24 weeks, with a favourable cost effectiveness ratio of €7,135/QALY gained. Other treatment response factors did not significantly influence cost effectiveness.

Sennfalt et al (10) compared 24 and 48 weeks of combination therapy with 48 weeks of IFN. They found that the two combination therapy regimens were associated with ICERs of $1,400 and $6,000 per discounted QALY gained, respectively, compared with IFN monotherapy for genotype 1 patients. For these patients, 48 weeks of combination therapy had an ICER of $9,800 per discounted QALY gained, compared with 24 weeks of treatment. For patients with other HCV genotypes, 24 weeks of combination therapy was cost saving compared with 48 weeks of combination therapy, and had an ICER of $1,800/QALY gained compared with IFN monotherapy. Because only very limited sensitivity analyses were undertaken, it was difficult to assess the effects of age, treatment efficacy and the natural history of the disease on ICERs in this CEA.

Stein et al (9) evaluated combination therapy, with a duration of 24 weeks (for patients with viral genotype 2 or

3) to 48 weeks (for genotype 1) versus IFN monotherapy. They found that the discounted ICER per QALY gained for combination therapy, compared with IFN monotherapy, was £3,485. Discounted cost per QALY gained was less for women aged younger than 40 years with HCV genotype 2 or 3 and moderate hepatitis than for patients with less favourable response characteristics, and varied from £872 to £8,626. Medication costs were more important than assumptions about disease progression or the cost of treating hepatitis C disease in the sensitivity analyses.

CONCLUSIONS FROM AVAILABLE STUDIES

Several findings have emerged from CEAs of treatment for hepatitis C infection:

- Marginal ICERs increase with the age of the patient, especially if there are unfavourable response characteristics or if IFN monotherapy is employed.

- The combination of IFN and ribavirin is more cost effective than IFN alone.

- It is useful to determine the HCV genotype when planning antiviral therapy: 24 weeks of combination therapy is more cost effective than 48 weeks for patients with genotype 2 or 3.

- The ICERs with combination therapy are very sensitive to the efficacy of treatment, which, in turn, is strongly affected by certain response characteristics. For example, in patients with unfavourable response characteristics (older male patient, genotype 1, high viral load and significant fibrosis [11]), combination therapy is associated with a high marginal ICER.

Future needs and unanswered questions

Pegylated IFN is more effective than the standard formulation and has recently been approved in North America and Europe for patients with HCV. When combined with ribavirin, it has become the treatment of choice for previously untreated patients with chronic HCV infection (12,13). Because both treatment costs and response rates increase with the use of pegylated IFN, CEAs would assist health care providers in deciding when to offer this agent. There are no published CEAs that compare pegylated with standard IFN available as yet.

There is some evidence, from posthoc analysis of the results from one clinical trial, that adjustment of the dose of ribavirin according to the patient's weight may be advantageous. Additional efficacy data are required before CEAs of weight-based versus fixed-dose ribavirin, in combination with pegylated IFN, can be undertaken.

Even though a CEA has found that 24 weeks of standard IFN plus ribavirin therapy is more cost effective than 48 weeks of treatment in patients with genotype 2 or 3 HCV infection (6), the optimum duration of treatment based on genotype requires further clarification. In addition, future CEAs need to use data on 'early stopping' rules from recent clinical trials. For example, discontinuation of treatment at 12 weeks in virological nonresponders has been recommended in partials receiving pegylated interferon and ribavarin (12,14).

There are no published studies on the cost effectiveness of antiviral therapy for patients who have not responded to either IFN alone or in combination therapy. Only one study has been published that assessed the cost effectiveness of IFN plus ribavirin in patients who had relapsed after IFN monotherapy (15). Relapsers and nonresponders constitute a significant proportion of HCV patients in clinical practice. CEAs can assist in the evaluation of several treatment options, including retreatment with IFN and ribavirin; retreatment with pegylated IFN and ribavirin; and the use of either 'maintenance' IFN or pegylated IFN. These therapeutic strategies are being investigated in large clinical trials, the results of which are essential for future CEAs.

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