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

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WR Kim. Motion – The available treatments for hepatitis C are cost effective: Arguments against the motion. Can J Gastroenterol 2002;16(10):710-715.

Hepatitis C is a prevalent infection in North America. However, the natural history of hepatitis C virus (HCV) infection in the general population is not fully understood. Available cohort-based studies suggest that only a relative minority of patients develop significant liver disease, such as cirrhosis and/or hepatocellular carcinoma. Other studies, mostly conducted based on referral patients with established disease, portray much more serious consequences of HCV infection. Although a substantial improvement has been made in the treatment for HCV, the overall impact of antiviral therapy in altering the natural course of HCV infection remains uncertain. Therapeutic trials involve narrow selection criteria that would exclude the majority of hepatitis C patients in the community, and are conducted in ideal settings that may not be generalizable to the average practice setting. Demographic groups that are at high risk of developing severe liver disease include older male patients who consume alcohol. In contrast, antiviral therapy is more effective in young and female patients and those who do not drink alcohol. Thus, patients who appear to be successfully treated may not be those for whom clearance of the virus would be beneficial. Cost-effectiveness studies published to date have not been able to fully address the complex and heterogeneous matrix of the factors that influence the natural history of HCV infection and treatment response.

In summary, there is a significant degree of uncertainty about many assumptions that are necessary in creating computer models to estimate the cost-effectiveness of HCV therapy. When interpreting the results of cost effectiveness analyses regarding the treatment of HCV infection, it is important to be aware of the underlying assumptions that are incorporated in the model and the data on which they are based. Given these limitations, vis-à-vis the expense, toxicity and yet limited effectiveness of the currently available antiviral agents, one should not blindly accept a conclusion that treatment for hepatitis C is cost effective.

Key Words: *Cost effectiveness; Hepatitis C*

Motion – Les traitements disponibles contre l'hépatite C sont rentables : Arguments contre la motion

L'hépatite C est une infection prévalente en Amérique du Nord. Toutefois, on ne comprend pas tout à fait l'évolution naturelle de l'infection au virus de l'hépatite C (VHC) au sein de la population générale. Les études de cohorte existantes laissent supposer que seule une minorité relative de patients développe une maladie hépatique importante, telle une cirrhose ou un carcinome hépatocellulaire. D'autres études, menées surtout auprès de patients en consultation atteints d'une maladie établie, présentent des conséquences beaucoup plus graves de l'infection au VHC. Bien que le traitement du VHC se soit amélioré considérablement, les répercussions globales des antiviraux pour modifier l'évolution naturelle de l'infection au VHC demeurent incertaines. Les essais thérapeutiques se fondent sur des critères de sélection étroits qui excluraient la majorité des personnes atteintes d'hépatite C au sein de la collectivité, et ils sont menés dans des environnements idéaux qui ne peuvent être généralisables

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This article was originally presented at a symposium entitled, "Controversies in Gastroenterology", sponsored by Axcan Pharma, Toronto, Ontario, April 8 to 10, 2002

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dans un cabinet moyen. Les groupes démographiques à haut risque de développer une maladie hépatique grave incluent les hommes âgés qui consomment de l'alcool. Pourtant, les antiviraux sont plus efficaces chez les femmes jeunes ou chez les personnes qui ne consomment pas d'alcool. Ainsi, les patients pour qui le traitement semble fonctionner ne sont peut-être pas ceux chez qui la clairance du virus serait bénéfique. Les études coût-efficacité publiées jusqu'à maintenant n'ont pu aborder toute la matrice complexe et hétérogène des facteurs qui influent sur l'évolution naturelle de l'infection au VHC et sur la réponse au traitement.

Pour résumer, il existe un degré important d'incertitude au sujet de nombreuses hypothèses nécessaires pour créer des modèles informatiques afin d'évaluer la rentabilité du traitement du VHC. Au moment d'interpréter les résultats des analyses coût-efficacité relatives au traitement de l'infection au VHC, il faut avoir conscience des hypothèses sous-jacentes du modèle ainsi que des données sur lesquelles ces hypothèses se fondent. Étant donné les restrictions reliées aux dépenses, à la toxicité et à l'efficacité limitée des antiviraux actuellement offerts, il ne faut pas accepter aveuglément la conclusion selon laquelle le traitement de l'hépatite C est rentable.

DETERMINANTS OF COST EFFECTIVENESS OF TREATMENT FOR HEPATITIS C

The two dimensions to consider in the economic analyses of health care interventions are health outcomes and costs. In the case of hepatitis C (HCV) infection, the relevant questions are thus as follows:

- What impact does the treatment of HCV have on health outcomes?
- What are the costs of treatment of HCV infection vis-a-vis potential savings from reduced morbidity and health care utilization in the future?

The impact of antiviral treatment on patients with hepatitis C is illustrated in Figure 1. The natural history of infection is represented in the upper panel. A proportion of patients with HCV develop clinically significant liver disease that results in overt illness, complications and premature death. These, in turn, lead to economic losses related to health care utilization and loss of productivity.

As shown in the lower panel, the application of effective treatment could alter the natural history of HCV infection. The proportion of patients who develop clinically important liver disease is decreased, which results in reductions in morbidity, mortality and economic losses. These benefits may be partially offset by costs and morbidity (adverse effects) associated with the treatment intervention.

The process of quantifying the costs and benefits of treatment for HCV requires accurate data in the following categories:

- the natural history of HCV infection and its impact on the health of the population, which may be measured in terms of shortened survival and/or reduced quality of life;
- the effectiveness of treatment in altering the natural history of the disease, namely prolongation of life and improvement in its quality;
- costs associated with morbidity and premature death, which result in health care utilization and loss of productivity;
- costs and morbidity (adverse effects) associated with the treatment itself.

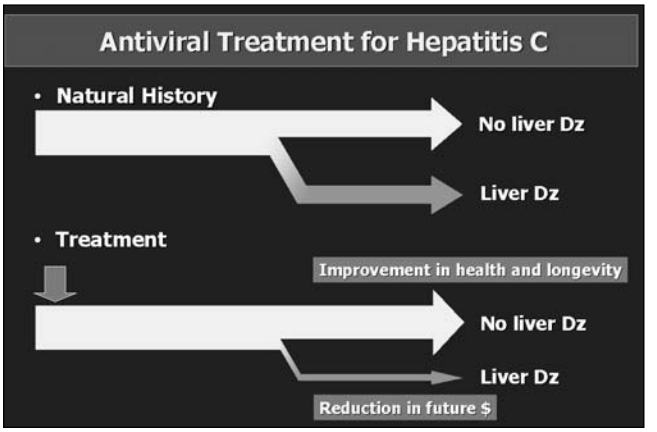

Figure 1) *Effective antiviral treatment reduces problems related to liver disease over time at a certain cost*

Some of these data are readily obtained, such as the cost of treatment, whereas others are difficult to estimate, such as reductions in morbidity and mortality by the institution of treatment. Much of the difficulty arises from the fact that HCV was only fairly recently recognized; thus, there are no long term data with which to directly evaluate treatment benefits. In lieu of long term data, investigators have developed various simulation models that have been used to estimate the future impact of HCV infection and its treatment. The results obtained thereby are fundamentally dependent on assumptions that are incorporated in the model. In the following sections, the potential sources of bias in these models that would lead to flawed conclusions about the cost effectiveness of treatment for HCV are discussed.

NATURAL HISTORY OF HCV INFECTION

Cost effectiveness analyses require quantitative estimates of the impacts of health intervention strategies on outcomes (1). The costs associated with treatment are then considered in comparison with the health benefits. Therefore, the larger the (net) effect, the smaller (better) the cost effectiveness ratio.

Uncertainties are inherent in any cost-benefit assessment. These can be decreased significantly by selecting groups of individuals whose prognosis can be predicted with precision. In Figure 2, three groups of HCV-infected persons are depicted schematically. Only a small number of persons with the infection, as represented by the apex of the

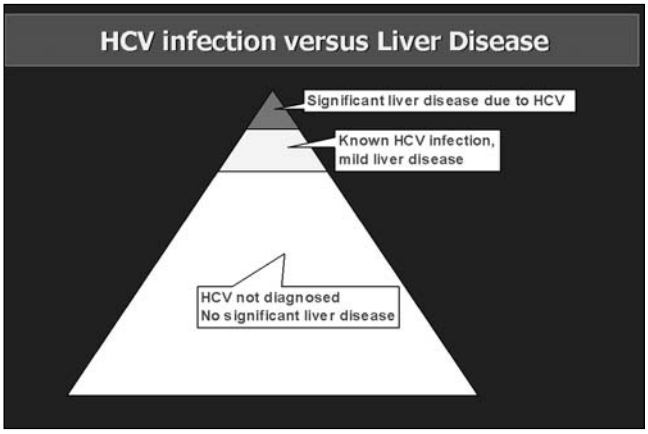

Figure 2) *Of all individuals with hepatitis C virus (HCV) infection, only a minority develop a significant liver disease*

triangle, develop significant liver disease from HCV and experience morbidity and/or mortality. The second tier includes persons with identifiable HCV, but in whom liver disease is not severe enough to cause clinical problems. The third group, which is thought to be the majority of cases, encompasses asymptomatic individuals whose HCV infection remains undetected.

During the third National Health and Nutrition Examination Survey (NHANES III), conducted between 1988 and 1994, a nationally representative sample of 21,000 subjects was tested for HCV (2). Of those tested, 380 people (1.8%) were found to have antibodies against HCV (anti-HCV), of whom 280 (74%) had detectable viral RNA in their serum. These data suggest that 3.9 million Americans (95% CI 3.1 to 4.8 million) have anti-HCV and 2.7 million Americans (95% CI 2.4 to 3.0 million) harbour circulating virus (HCV-RNA) in their bloodstreams. This would make HCV the most prevalent blood-borne infection in the United States (3).

While the NHANES study provided information about the prevalence of HCV infection, it was unable to evaluate the frequency and severity of liver disease in infected persons. Alanine aminotransferase levels were not measured in serum samples because of concerns that the manner in which they were stored may have resulted in enzyme degradation (2).

It is well recognized that not all HCV-positive individuals develop significant liver disease (4,5). In fact, prospective studies of the natural history of HCV have shown that most infected subjects remain asymptomatic and unaware of the infection (6-8).

Seeff et al (7) used serum samples that had been obtained from 8568 military recruits between 1948 and 1955, of whom 34 (0.4%) were positive for HCV. Clinical outcomes data were obtained from a variety of sources, including the Health Care Financing Administration, the Department of Veterans Affairs and the National Death Index. During the 45 years of follow-up, liver disease occurred in 12% of persons with HCV, compared with 2.4% of HCV-negative subjects. The relative risk was 3.6 (95% CI 0.9 to 13.5), which was not statistically significant. The death rates were 41% and 26%, respectively, with a relative risk of 1.5 (95% CI 0.8 to 2.6), which was, again, not significantly different. Moreover, only one death in the HCV-positive cohort could be attributed to liver disease. Similarly, studies have shown that the vast majority (83% to 97%) of women who contracted HCV from contaminated immunoglobulins did not develop significant hepatic fibrosis, and no more than 2% had cirrhosis (6,8).

In contrast to these longitudinal studies involving prospective cohorts, the majority of investigations into the natural history of HCV-related liver disease have been conducted at specialty medical centres and were based on patients with established disease, including those undergoing liver transplantation (9-14). Such studies of referral populations tend to overemphasize serious consequences of infection, including decompensated cirrhosis and hepatocellular carcinoma. In one study, 131 patients with post-transfusion HCV were evaluated (10). After approximately two decades of follow-up, 23% had chronic active hepatitis, 45% had cirrhosis and 11% had hepatocellular carcinoma.

The discrepancies in the foregoing results underscore the importance of accurately defining the study population. Imputing the outcome of HCV infection in the overall population using data derived from referral samples leads to biased conclusions. If such data were used to formulate health policy, the impact of the infection on the health of individuals would be overestimated. On the other hand, the prognosis of HCV infection in the general population remains largely unknown.

As of 2001 in the United States, even the most basic elements of public health data, such as mortality related to HCV, are lacking. It is widely quoted that 8000 to 10,000 deaths may be attributed to HCV-related liver disease in the United States each year. The evidence for this figure is weak. It was based on expert consensus estimates that, of approximately 25,000 liver-related deaths in the United States, up to 40% may be related to HCV (15). While this is likely an overestimate, the figure may still be used to calculate the time interval between the onset of infection and death. If there are 8000 to 10,000 deaths among 2.7 million infected persons each year, this translates into an annual mortality rate of 0.3% to 0.4%. This, in turn, means that the average disease duration (prevalence divided by death rate) is between 270 and 337 years, which suggests that only a small fraction of individuals with HCV infection develop and succumb to significant liver disease.

Currently, data do not support the universal application of HCV treatment within the general population. If only a small minority of people with HCV infection are likely to suffer serious consequences, it is not reasonable to expend health resources to treat everyone who is infected. Instead, it is more appropriate to identify subgroups of people who are at the most risk of developing problems.

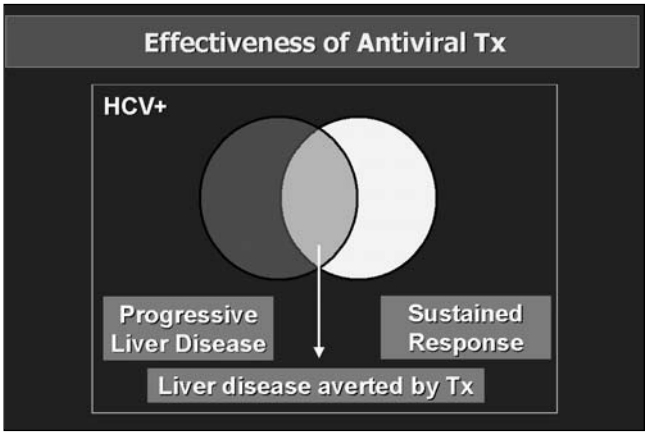

Figure 3) *The degree of overlap between people who would have progressive liver disease and those who would have sustained response determines the effectiveness of antiviral treatment*

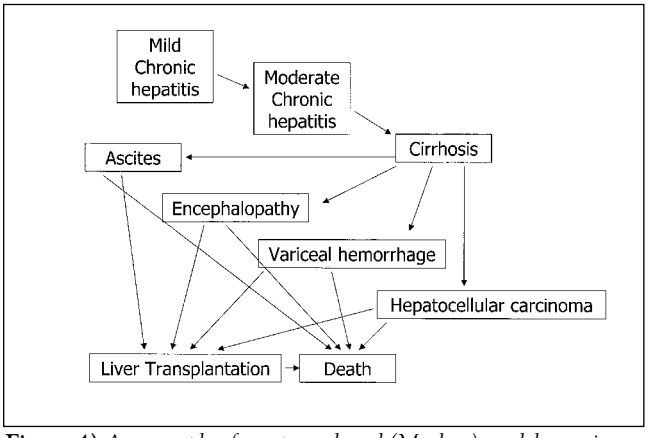

Figure 4) *An example of computer-based (Markov) model to estimate the long term outcome of Hepatitis C with and without treatment*

EFFECTIVENESS OF ANTIVIRAL TREATMENT

Effectiveness versus efficacy

Health care interventions are considered effective to the extent that they improve health in real practice settings. Thus, *effectiveness* must be distinguished from two closely related concepts. *Efficacy* denotes how well the intended objectives are achieved in ideal settings, which are often academic or research environments in which services or treatments are developed or initially tested. *Appropriateness* reflects the broader range of issues that are considered in deciding whether an intervention should be done, including assessments of the extent to which the expected health benefit exceeds the expected negative consequences of the intervention, as well as considerations of acceptability, feasibility and costs (1).

Virtually all of the cost effectiveness analyses that have been undertaken to date on the treatment of HCV have used data obtained from randomized controlled trials (RCTs) to estimate the effectiveness of antiviral treatment. Results from such trials reflect more closely the efficacy of the intervention than its effectiveness. The primary disadvantages of using efficacy and side effect data from RCTs include the select nature of the subjects, the differences between the performance of the intervention in investigational settings and in clinical practice, and the limited time horizon that is employed.

RCTs usually enroll a narrowly defined subset of patients. While this allows the investigators to come to specific and precise conclusions, the patients who are studied are usually not representative of the range of subjects present in the general population, or even the typical subject with the disorder. The healthy volunteer effect is a well-known phenomenon, whereby patients who consent to participate in a study may also have better than average health outcomes. Many HCV patients in the community experience problems with substance abuse and/or mental health, and these problems interfere with or even preclude antiviral therapy. For example, of 293 HCV-RNA-positive patients seen at a teaching county hospital in Ohio over a two-year period, only 28% were eligible for treatment. The remaining 72% were not treated for the following reasons: 37% did not adhere to evaluation procedures, 34% had medical or psychiatric contraindications, 13% had ongoing substance or alcohol abuse, 11% preferred no treatment, and 5% had normal liver enzyme levels. Finally, in RCTs published to date, racial minority groups, in whom the prevalence of HCV is the highest, have been under-represented, raising further doubts about the generalizability of their results.

The ideal conditions for implementing an intervention, which are exemplified in an RCT, are rarely duplicated in the practice settings where the vast majority of clinical care is provided. Such trials are designed to include sufficient personnel and attention to follow-up and monitoring to minimize the number of patients who withdraw from therapy and to maximize compliance with the research protocol. Consequently, results that are reported in an RCT generally overestimate the 'true' effectiveness of the intervention.

Timeframe of available data and overlapping risk factors

Another difficulty with using RCT data to estimate the effectiveness of an intervention is that the time horizon of RCTs is usually quite limited. In RCTs conducted for HCV therapy, the usual end point is a sustained virological response, or virological cure, which is obviously an important therapeutic outcome. These studies do not, however, provide data about the effectiveness of treatment in preventing the development of decompensated liver disease or decreasing mortality rates. Such long term projections require the use of mathematical models or simulations that are based on a number of assumptions.

Figure 3 illustrates the relationship between morbidity from liver disease and the elimination of HCV by antiviral therapy. The gray circle represents the population of subjects who are 'destined' to develop HCV-related progressive liver disease, with resultant morbidity and mortality. The white circle denotes the population of subjects in whom antiviral therapy would eliminate the virus. The left-hand

panel depicts a hypothetical scenario in which the two circles do not overlap, indicating that all of the sustained responders belong to the group of patients who would not have developed significant chronic liver disease. In such a situation, there would be no benefit whatsoever from antiviral therapy, and this treatment would have no effect on reducing long term morbidity. Hence, the cost effectiveness ratio would be infinite.

Perhaps the more realistic situation is illustrated in the right-hand panel, in which a proportion of the sustained responders would otherwise have developed chronic liver disease. Thus, some of the subjects would benefit from the elimination of the HCV with antiviral therapy. The most optimistic viewpoint would be represented by a complete overlap of the two circles, implying that the development of chronic liver disease could be entirely prevented by antiviral therapy and that all sustained responders realize a substantial benefit. This last scenario is highly unlikely to reflect reality.

Evidence suggests that the overlap between the progressive liver disease and sustained response populations is probably small. For example, one study of the rate of progression of hepatic fibrosis identified older age, male sex and alcohol consumption as risk factors for advanced fibrosis (17). Other HCV studies have confirmed that these are poor prognostic factors for the development of cirrhosis (12,13,18-20). In contrast, Poynard et al (21) reported that, based on studies of 1744 patients, young (under the age of 40 years) female patients experience a better response to treatment with a combination of interferon and ribavirin, independent of the duration of treatment, baseline viral load, viral genotype and degree of fibrosis. Virtually all RCTs in HCV treatment have excluded patients with active alcohol dependence, whereas limited data suggest that even moderate consumption of alcohol (more than two alcoholic beverages per day) significantly interferes with treatment response (22).

An interesting dichotomy is apparent: older male patients who consume alcohol are more likely to develop progressive liver disease and are generally less likely to respond to treatment. Therefore, the patients who respond best to antiviral treatment are demographically distinct from those with the greatest risk of developing chronic liver disease, which means that the two circles in Figure 3 tend to diverge.

ECONOMIC IMPACT OF HCV

Because HCV was identified only recently, the economic impact of this pathogen has not been well documented. A widely quoted estimate of the financial burden of HCV in the United States is $600 million annually (23). In our recent analysis, the expenditure for inpatient care alone of liver-related problems associated with HCV may have been as high as $514 million in 1995 (24). This figure does not include major costs such as professional fees and outpatient expenses.

Another major component of the burden of HCV is indirect costs, including lost earnings due to illness, hospitalization and premature death. The illness tends to impair work productivity and, because it mainly affects persons in their 30s and 40s, the true economic impact may exceed that due to the chronic illnesses that afflict older populations. We estimated that inpatient care accounted for only one-third of all costs, the remainder being outpatient and indirect costs. Thus, the economic burden attributable to HCV may have been as high as $1.5 billion in 1995, or $500 annually for each of the three million Americans who are infected with the virus.

It remains uncertain what proportion of the health care expenditures for HCV patients can be attributed to the infection itself, and how much can be attributed to important comorbidities such as substance abuse and mental health problems. It is important to determine the relative importance of these factors because measures to prevent the transmission of the virus and to eradicate the infection at an early stage would be expected to reduce only the costs that are due to HCV itself (25).

STRENGTH OF EVIDENCE FOR COST EFFECTIVENESS OF HCV TREATMENT

The conclusions from cost effectiveness analyses based on computer models are fundamentally dependent on the assumptions that are employed. Figure 4, which is based on a published analysis by Buti et al (26), illustrates the complexity of these simulations. Treatment with interferon and ribavirin was evaluated in a hypothetical cohort of previously untreated patients with chronic HCV. Each arrow represents a transition from one health state to another, the annual likelihood of which is designated by a quantitative estimate. There is substantial uncertainty in each of these assumptions, which is compounded when one considers the model as a whole.

Other failings of these models have already been discussed. The natural history of disease that is assumed in the analysis might not be generalizable to the population to which the analysis is applied. Moreover, little consideration is given to the overlap between factors that are associated with the rapid progression of liver disease and with a lack of response to antiviral therapy.

In summary, the cost effectiveness of treatment for hepatitis C is primarily dependent on the natural history of the infection and the effectiveness of treatment in altering it.

Because the population of individuals infected with HCV is heterogeneous, the cost effectiveness of treatment varies widely and patient selection is critically important in optimizing the outcome of treatment. The cost effectiveness of antiviral therapy is more favourable in patients in whom the likelihood of progression of liver disease is high and in whom the likelihood of treatment response is high. Examples of these patients may include those infected with genotypes 2 and 3 or those with advanced fibrosis. Under the current circumstance in which the natural history in an individual patient remains uncertain and available therapeutic agents are expensive, toxic and yet still not very effective, one should not blindly accept a conclusion that treatment for HCV is cost effective.

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