Economic evaluation of chronic hepatitis C treatment by interferon-ribavirin combination therapy in Belgium

Jean Delwaide

Service de Gastro-entérologie, CHU Sart Tilman , 4000 Liège.

Abstract

With present treatments for chronic hepatitis C by the combination of interferon alpha and ribarivin, it is possible to obtain a sustained viral response in a large number of patients. This viral response is associated with long-term disappearance of the C virus, improvement of histology, improvement in quality of life and, most than likely, a reduction in the risk of premature death or infection-linked complications. This therapy is, however, expensive and the number of potentially treatable patients is high in view of the relatively high prevalence of the disease in the population. An economic evaluation is thus indispensable in order, on the one hand, to assess the cost-effectiveness ratio of the treatment (i.e. the extra cost to be paid for obtaining the greater effectiveness provided by the therapeutic combination in comparison with absence of treatment or treatment by interferon alone), and, on the other hand, to estimate practically the global cost of treatment for Belgium (i.e. the annual expense for society according to the number of patients treated per year). (Acta gastroenterol. belg., **2002**, 65, **233-236**).

Key words : hepatitis C , interferon alpha , ribavirin, cost-effectiveness, health care, qaly.

Introduction

In order to consider the economic evaluation of a therapy, certain data are requested. The prevalence, the natural history of the affection and the effectiveness of therapies must be known. Furthermore, for the economic evaluation to be useful in practice, standard therapeutic strategies have to be proposed by consensus conferences, and these recommendations should be followed by the majority of doctors concerned.

Prevalence and natural history of chronic hepatitis C

The estimated prevalence of the C virus infection in Belgium is 0.87% (1). The majority of patients have been contaminated by intra-venous drug injection, by transfusion carried out before systematic screening for HCV antibodies in blood-donors (before July 1990), more rarely from an invasive medical examination, tattooing, chronic haemodialysis and perhaps through sexual relations (2). Spontaneous resolution of the infection is rare, and in roughly 80% of contaminated individuals the infection persists. Chronic hepatitis C can lead to cirrhosis in 20% of cases over a period of about 20 years. It is estimated that the cirrhosis leads to hepatic decompensation in 3.9% of patients a year and to hepatocellular carcinoma in at least 1.4% of patients a year (3). Certain factors are associated with a more rapid progression of fibrosis, such as male gender, alcohol abuse, older age at the time of contamination, disease duration, higher necroinflammatory grade at the time of the biopsy, co-infection with hepatitis B or HIV virus. More precise prognosis of individual patient's risk is easier if fibrosis is already present on the initial biopsy (3% progression per year towards cirrhosis in patients with low-grade fibrosis, 25% a year in patients with precirrhogenous fibrosis) (4). Nevertheless, in practice, for a given patient with an early affection, it is difficult to evaluate the long-term prognosis.

Economic evaluation of the combination of interferon α-2b and ribavirin

Effectiveness of therapies

Considerable progress has been made in the last few years in the care of patients with chronic C virus infection.

The main therapeutic objective is to obtain a sustained viral response (SVR), in which HCV-RNA remains undetectable for 6 months after therapy is completed. It has been shown that the achievement of a SVR was closely correlated with a long-term disappearance of the virus, an improved histology, an improved quality of life, and most than likely, a reduction of the risk of premature death.

The combination of interferon and ribavirin achieves this therapeutic objective considerably more often than with interferon treatment alone. Two large registry trials carried out in Europe and the U.S.A. (5, 6) have shown a rate of SVR in patients treated with interferon α-2b plus ribavirin of 31 to 35% after 24 weeks (wk) of therapy and 38 to 43% after 48 wk (instead of 13 and 19% after respectively 24 wk and 48 wk of interferon treatment alone). For still unclear reasons, patients infected by a C virus of genotype 2 or 3 (present in 25% of patients in Benelux (7)) respond better to the therapy than patients infected by C virus of type 1. In the case of infection by a 2 or 3 genotype, interferon-ribavirin treatment gives an SRV of 69% after 24 wk, 66% after

Corresponding author : Jean Delwaide, Service de Gastroentérologie, CHU Sart Tilman, 4000 Liège, Belgium. E-mail : gastroentero@ulg.ac.be.

48 wk, whereas in the case of infection by the 1 genotype, the therapeutic combination gives only 16% SRV after 24 wk and 28% after 48 wk (7% for interferon alone). Pretreatment HCV-RNA level less than 2 million copies/ml (or 800 000 UI/ml), absence of cirrhosis and female gender are also favourable predictive characteristics of response. It is important to note that even patients with a cirrhosis can eliminate the C virus with the therapeutic combination (SVR in 17% of patients) (8).

In the light of these data, it is at present recommended (9) to treat patients by the therapeutic combination. The optimal duration of treatment is 48 wk in patients with C virus of genotype 1 and 24 wk for patients with C virus of genotype 2 or 3.

It is important in the economic evaluation of treatment to consider that 20% of patients interrupt the treatment prematurely due to the appearance of side-effects (essentially insomnia, depression, irritability, anaemia). Finally, treatment should be discontinued in patients with genotype 1 infection who have detectable viremia at 24 wk because further therapy is unlikely to achieve a SVR.

Interferon α-2b + Ribavirin 48 weeks versus 24 weeks	Cost-effectiveness
All patients	7 700 $/QALY
Genotype 1	2 500 $/QALY
Genotype 2 or 3	> 50 000 $/QALY
Woman, < 40 yr old, viral load < 2 million, and no septal fibrosis	> 50 000 $/QALY
PCR still positive after 24 weeks	74 000 $/QALY

Fig. 1. — Cost effectiveness of combination therapy during 48 weeks versus 24 weeks in different sub-groups of patients (adapted from Wong *et al.*).

Ratio > 50 000 $/QALY are considered to be non cost effective.

Cost-effectiveness ratio evaluation

The combination of interferon-ribavirin is expensive, from € 11.695 to € 13.405 (for a 48 wk treatment with interferon α-2b 3 million units 3 times a week, plus either 5 or 6 ribavirin tablets a day, according to the body weight).

An economic evaluation is thus essential for such expensive therapies. Cost-effectiveness studies make it possible to determine, in comparison with a reference strategy (for example absence of treatment or interferon treatment alone), the extra cost necessary for obtaining better effectiveness. The better effectiveness is expressed by the number of years of life gained, moderated by a quality of life index (QALY). A cost-effectiveness ratio of up to $ 50.000/QALY (i.e. the cost of one year of life gained by dialysis) is generally considered acceptable.

Two studies (10, 11) have shown that the interferon-ribavirin combination has a very acceptable cost-effectiveness ratio in comparison with no treatment or interferon treatment alone. Wong's (10) study presents the advantage of having used the data from the two registry trials (5, 6) which served to establish the current treatment recommendations. The data concerning the 1744 patients enrolled in these studies have been placed on a computer programme which allows a prediction of long-term clinical and economic outcomes of each therapeutic arm studied (interferon-ribavirin 24 or 48 wk, interferon alone 24 or 48 wk). This study shows that combined interferon-ribavirin treatments carried out for 24 and 48 wk present an excellent cost-effectiveness ratio in comparison with a 48 wk treatment by interferon alone (cost-effectiveness ratio of $ 4. 400 /QALY for a treatment of 24 wk and $ 5.400 /QALY for a treatment of 48 wk). The extra costs caused by the use of ribavirin are thus practically compensated for by the greater probability of obtaining a sustained viral response leading to a reduction in costs related to the evolution of the hepatic affection. As to optimal duration of treatment (fig. 1), the 48 wk therapeutic combination presents a very acceptable cost-effectiveness ratio in comparison with the 24 wk treatment ($ 7.700 /QALY) for the large majority of patients, except for patients with genotype 2 or 3, or for the small number of patients presenting four favourable treatment response factors (woman, age < 40, viral load < 2 million copies/ml, and no septal fibrosis). However, in the case of persisting viral infection detectable at the 24th week of treatment, the continuation of combined treatment up to the 48th week presents a cost-effectiveness ratio of $ 74.800 /QALY. Stopping treatment in viral non-responders at the 24th week thus seems to be the most economically effective strategy when a 48-week treatment was initially planned. Finally, a sensitivity analysis has shown that the cost-effectiveness ratio of the interferon-ribavirin combination for 48 wk against the absence of treatment was also excellent (3.200 $/QALY). It has been shown, also, that the combination therapy would remain cost-effective even if the likelihood of liver disease progression was one-third of the baseline probabilities.

As well, Younossi *et al.* (11), using a different model (hypothetical cohort of patients all with the same initial characteristics, treated by different strategies) demonstrated the favourable cost-effectiveness ratio of immediate treatment by interferon and ribavirin rather than by interferon alone or an initial treatment by interferon alone, followed, in the case of non-response or relapse by the combined treatment. He also demonstrated that

the strategy determined by the genotype, combined treatment for 48 wk for genotype 1 and 24 wk for genotypes 2 and 3, presented the best cost-effectiveness ratio.

Evaluation of global cost of treatment for Belgium

This is relatively easy for our country to evaluate the global cost of treatment since the number of patients treated annually is roughly known. Ribavirin has, indeed, only been refunded in Belgium since July 2001. Until then, the great majority of patients was treated within the framework of Belgian protocols, under the auspices of the Belgian Association for the Study of the Liver, offering patients the possibility of being treated by bitherapy. It is estimated that roughly 700 patients a year have been treated in Belgium by interferon-ribavirin combination in the last few years. It is not surprising that so few patients are treated in regards of the disease prevalence. It has been shown recently that 70% of patients evaluated for therapy are finally not treated for different reasons (either because they do not adhere to evaluations procedures, or have medical or psychiatric contraindications, or have ongoing substance or alcohol abuse, or prefer no treatment, or have normal transaminases) (12).

If classic therapeutic recommendations are followed, of these 700 patients, 25% (175) patients with a genotype 2 or 3 would have to be treated for 6 months. Patients with a genotype different from 2 or 3 (525 patients) would have to be treated for one year on condition that the PCR screening for C virus is negative after the first 6 months of treatment (50% of these, or 262 patients (according to 5, 6)). On the basis of this approximation, the number of patients treated per year for 6 months would be 437 (175 + 262), those treated for 1 year – 263 (fig. 2).

The annual cost of a treatment with interferon α-2b plus ribavirin according to these approximations would be of about € 5.6 to 6.5 million. A budget of this size has been judged acceptable by the INAMI/RIZIV. The actual cost is in fact lower if we consider that 20% of patients treated for 48 weeks have to stop the therapeutic treatment owing to the appearance of side-effects or poor tolerance.

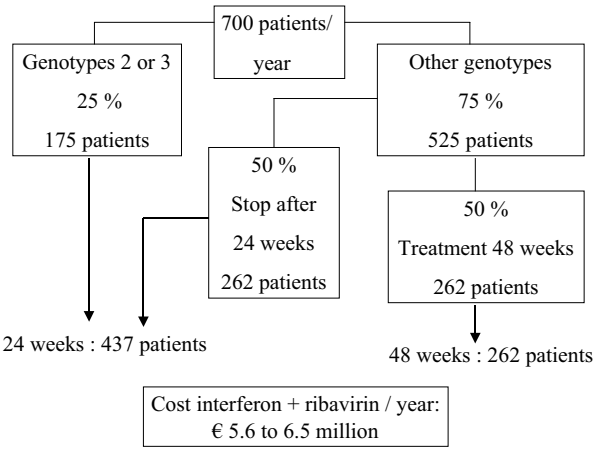

Fig. 2. — Estimation of the annual cost of the combination therapy with interferon α-2b plus ribavirin in Belgium.

The estimated total number of patients treated yearly (700) is based on the experience of the previous years. A majority of the patients (75%) are suffering from a viral genotype 1 and should be treated for 48 wk. Half of these patients, however, will stop the treatment after 24 wk due to a non response to therapy. In consequence, most of the patients (genotype 2 or 3 patients, and genotype 1 patients non responding to therapy) are expected to be treated during 24 wk. On that basis, the annual cost of the combination therapy can be estimated to € 5.6 to 6.5 million per year, in Belgium.

Economic evaluation of the combination of pegylated interferon α-2b plus ribavirin

Conjugation of polyethylene glycol (peg) to interferon is the newest advance in the treatment of hepatitis C. Pegylation increases the elimination half-life of interferon, providing improved efficacy with once weekly dosing. With a treatment of peginterferon α-2b 1.5 μg/kg each week plus 800 mg/day ribavirin for 48 weeks, sustained viral responses of 42% for genotype 1 infection and 80% for genotype 2 and 3 infections are reached (13). It has been calculated retrospectively that if the dose of ribavirin in association with peginterferon was adapted to the body weight, a sustained viral response of 48% for genotype 1 and 88% for genotype 2 or 3 could be reached (13). Prospective studies are in progress to confirm this retrospective evaluation.

Peginterferon, however, will cost 2.5 times more than unmodified interferon. A 48-weeks treatment with peginterferon α-2b 1.5 μg/kg plus ribavirin according to the body weight will have a cost of € 16.900 (< 65 kg), € 20.520 (65-85 kg), € 25.100 (> 85 kg). Wong and Nevens have recently published a cost-effectiveness evaluation of the combined therapy with peginterferon α-2b or with unmodified interferon α-2b as initial treatment of chronic hepatitis C in Belgium (14). The cost-effectiveness ratio of combined therapy with peginterferon versus no treatment was € 3.021/QALY. Compared to combined therapy with unmodified interferon, the cost-effectiveness ratios of combined therapy with peginterferon were € 7.111 for the overall population, € 4.748 for genotype 1, 4 or 5 infections and € 13.841 for genotype 2 or 3 infections. These results suggest that peginterferon α-2b plus ribavirin is cost-effective when compared to other well-accepted medical interventions.

Peginterferon should replace soon unmodified interferon formulations with a reimbursement accorded for genotype 1 and non 2 or 3 infections, for which the advantage of the peg formulation is the most evident.

Finally, it remains to determine the global annual cost for the 700 treated patients a year in Belgium with this strategy (peginterferon α-2b 1.5 μg/kg each week plus

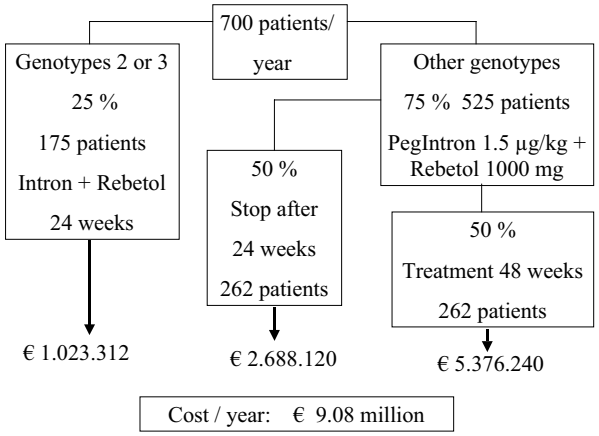

Fig. 3. — Estimation of the annual cost of the combination therapy with peginterferon α-2b plus ribavirin in Belgium.

The estimation is based on body weight of 70 kg (estimations for body weight < 65 kg, or 85 kg are in the text).

ribavirin 800-1200 mg/d for 48 weeks in case of genotype 1, 4 or 5 infections, and with unmodified interferon α-2b thrice a week plus ribavirin 800-1200 mg/d for 24 weeks in case of genotype 2 or 3 infections). According to the repartition of cost described in fig. 3, it can be predicted that the total cost per year will be € 9.087.672 if the weight of all the patients was 70 kg (€ 7.665.012 and € 10.887.612 if the weight was < 65 kg or > 85 kg, respectively). If patients with genotypes 2 or 3 were treated for 24 weeks with peginterferon and ribavirine instead of unmodified interferon plus ribavirin, the additional cost would be of € 777.188.

Prospects

The present combination of interferon-ribavirin presents a cost-effectiveness ratio within the norm of what is generally accepted in economic studies.

These economic calculations are based, however, on uncertain data : the exact natural history of the affection is not known ; not all patients are treated in accordance with the recommendations of the consensus conferences ; the number of patients to be treated may rise considerably in the future owing to better screening for the illness or wider information on therapeutic effectiveness. Re-evaluation has thus to be considered if a parameter changes.

Acknowledgement

The author thanks Mr Johan Eykens, Public Affair Manager Benelux, Schering-Plough Benelux, for the information concerning the estimated future price of peginterferon α-2b and for his review of the calculations.

References

1. BEUTELS M., VAN DAMME P., AELVOET W., DESMYTER J., DONDEYNE F., GOILAV C., MAK R., MUYLLE L., PIERARD D., STROOBANT A., VAN LOOCK F., WAUMANS P., VRANCKX R. Prevalence of hepatitis A, B, and C in the Flemish population. *European Journal of Epidemiolog*, 1997, **13** : 275-280.
2. DELWAIDE J., BOURGEOIS N., COLLE I., ROBAEYS G. Risk factors for hepatitis C : past, present and future. *Acta Gastroenterol. Belg.*, 2002, **65** : 87-89.
3. FATTOVITCH G., GUISTINA G., DEGAS F. Morbidity and mortality in compensated cirrhosis type C : a retrospective follow up study of 384 patients. *Gastroenterology*, 1997, **112** : 463-472.
4. YANO M., KUMUDA H., KAGE M., IKEDA K., SHIMAMATSU K., INOUE O., HASHIMOTO E., LEFKOWITCH J., LUDWIG J., OKUDA K. The long-term pathological evolution of chronic hepatitis C. *Hepatology*, 1996, **23** : 1334-1340.
5. MC HUTCHISON J., GORDON G., SCHIFF E., SHIFFMAN M., LEE W., RUSTGI V., GOODMAN Z., LING M, CORT S., ALBRECHT J. for the Hepatitis Interventional Therapy Group. Interferon alpha2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N. Engl. J. Med.*, 1998, **339** (21) : 1485-1492.
6. POYNARD T., MARCELLIN P., LEE S., NIEDERAU C., MINUK G., IDEO G., BAIN V., HEATCOTE J., ZEUZEM S., TREPO C., ALBRECHT J., for the International Hepatitis Interventional Therapy Group. Randomised trial of interferon alpha 2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha 2b plus placebo for 48 weeks for treatment of chronic hepatitis infection with hepatitis C virus. *Lancet*, 1998, **352** : 1426-1432.
7. KLETER B., BROUWER J., NEVENS F., VAN DOORN L., ELEWAUT A., VERSIECK J., MICHIELSEN P., HAUTEKEETE M., CHAMULEAU R., BRENARD R., BOURGEOIS N., ADLER M., QUINT W., BRONKHORST C., HEIJTINK R., HOP W., FEVERY J., SCHALM S., the Benelux Study Group on Treatment of Chronic Hepatitis C. Hepatitis C virus genotypes : epidemiological and clinical associations. *Liver*, 1998, **18** : 32-38.
8. SCHALM S., WEILAND O., HANSEN B., MILELLA M., LAI M., HOLLANDER A., MICHIELSEN P., BELLOBUONO A., CHEMELLO L., PASTORE G., CHEN D., BROUWER J., and the EUROHEP study group for viral hepatitis. Interferon-ribavirin for chronic hepatitis C with and without cirrhosis : analysis of individual patient data of six controlled trials. *Gastroenterology*, 1999, **117** : 408-413.
9. EASL International Consensus Conference on Hepatitis C. Consensus statement. *J. Hepatol.*, 1999, **30** : 956-961.
10. WONG J., POYNARD T., LING H., ALBRECHT J., PAUKER S. on behalf of the International Hepatitis Interventional Therapy Group. Cost-effectiveness of 24 or 48 weeks of interferon alpha 2b alone or with ribavirin as initial treatment of chronic hepatitis C. *Am. J. Gastroenterol.*, 2000, **95** : 1524-1530.
11. YOUNOSSI Z., SINGER M., MCHUTCHISON J., SHERMOCK K. Cost-effectiveness of interferon alpha 2b combined with ribavirin for the treatment of chronic hepatitis C. *Hepatology*, 1999, **30** : 1318-1324.
12. FLACK-YTTER Y., KALE H., MULLEN K., SARBAH S., SORESCU L., MC CULLOUGH A. Surprinsingly small effect of antiviral treatment in patients with hepatitis C. *Ann. Intern. Med.*, 2002, **136** : 288-292.
13. MANNS M., MC HUTCHISON J., GORDON S., RUSTGI V., SHIFFMAN M., REINDOLLAR R., GOODMAN Z., KOURY K., LING M., ALBRECHT J., and the International Interventional Therapy Group. *Lancet*, 2001, **358** : 958-965.
14. WONG J., NEVENS F. Cost-effectiveness of peginterferon alfa-2b plus ribavirin compared to interferon alfa-2b plus ribavirin as initial treatment of chronic hepatitis C in Belgium. *Acta Gastroenterol. Belg.*, 2002, **65** : 100-111.