

A pragmatic and cost-effective strategy of a combination therapy of interferon alpha-2b and ribavirin for the treatment of chronic hepatitis C

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Background Combination of interferon (IFN) alpha and ribavirin is considered the standard treatment for patients with chronic hepatitis C. While combination therapy is more effective than IFN alone, the optimal management of combination treatment remains uncertain.

Objective To assess a pragmatic and cost-effective strategy for the therapy of treatment-naive patients with chronic hepatitis C.

Design Markov model on original data of two randomized trials.

Methods A validated computer simulation model was applied to non-cirrhotic hepatitis C virus (HCV)-infected patients. Patient characteristics and efficacy of treatment were extracted from two randomized trials reporting on 1445 non-cirrhotic patients. Different strategies were compared separately for genotype 1 and genotype non-1 (mostly genotype 2/3) infections: (1) no treatment; (2) IFN for 48 weeks (if at 12 weeks HCV RNA undetectable); (3) IFN and ribavirin for 24 weeks; (4) IFN and ribavirin for 48 weeks; (5) IFN and ribavirin for 48 weeks (if at 24 weeks HCV RNA undetectable). All strategies were tested for different combinations of known response factors.

Results In genotype non-1 infection, 24 weeks of

combination therapy dominates all other strategies. In genotype 1 infection, 48 weeks of combination therapy for week-24 responders only prolongs life expectancy at a favourable cost-effectiveness ratio (CE) of 7135 euros per quality-adjusted life year (QALY). Taking response factors other than genotype into account does not add to the effectiveness or cost effectiveness.

Conclusion Treating non-cirrhotic patients with chronic hepatitis C according to genotype only is most cost effective independent of the number of other known response factors. *Eur J Gastroenterol Hepatol* 13:483–488 © 2001 Lippincott Williams & Wilkins

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Introduction

People infected with hepatitis C virus (HCV) will develop chronic hepatitis in 80% of cases [1,2]. Most studies report a risk of 10–20% of developing cirrhosis over a period of 20–30 years [2–5]. With established cirrhosis, the annual risk of developing hepatocellular carcinoma (HCC) rises considerably to 1–5% [6,7].

Until recently, 48 weeks of interferon (IFN; 3 million units subcutaneously three times a week) was the only effective strategy for the treatment of chronic hepatitis C, with sustained response rates (SR) reaching only 15–20% [8]. Although IFN is costly, the cost-effectiveness ratio (CE) for IFN falls within the limit of other well accepted therapies [9–11]. Recent randomized trials have shown a higher effectiveness of a combina-

tion of interferon alpha-2b with ribavirin (IFN-R; IFN 3 MIU sc TIW and ribavirin 1000/1200 mg orally once daily) [12–14] versus IFN alone.

Although combination therapy is more costly than therapy with IFN alone, Younossi *et al.* [15] have shown a favourable CE of IFN-R compared with IFN. The most favourable strategy was to perform viral genotyping to determine the duration of IFN-R with genotype 1 patients receiving 48 weeks of IFN-R and all others receiving 24 weeks of therapy. Wong *et al.* [16] also demonstrated a favourable CE of IFN-R.

Poynard *et al.* [17] confirmed IFN-R as the first-line treatment of chronic hepatitis C, and introduced five favourable independent response factors that are asso-

ciated with a sustained response: genotype 2 or 3, baseline viral load less than 3.5 million copies/ml, no or portal fibrosis only, female gender, and age less than 40 years. Those patients who are HCV-negative at week 24 and have less than four favourable response factors should be treated for an additional 24 weeks. Poynard *et al.* argued that an approach that considered only virological characteristics (as suggested by Younossi *et al.* [15]) might be an oversimplification and may lead to wrong treatment decisions in certain patient subgroups.

The aim of our study was to assess and optimize the CE of different schemes of combination therapy with IFN-R. This evaluation, reflecting actual treatment patterns and costs, was aimed at finding a pragmatic, cost-effective strategy for treatment of patients with chronic hepatitis C.

Methodology

Using standard decision analysis software (Decision Maker 7.0 [18]), we applied an already established and validated computer simulation model [9,19]. The model is based on a Markov simulation of the natural history of hepatitis C. Cohorts of patients move through predefined health states over time until all patients have entered the dead state. Patients may progress over time by given transition probabilities to more advanced disease states or death. Morbidity and mortality from hepatitis C, and mortality from other causes as occur in the general Swiss population, were considered. The original model was extended to include therapeutic options for HCC (orthotopic liver transplantation and partial hepatectomy), reflecting current treatment modalities [20].

Because viral genotype is the most important independent response factor [13,14] and is usually determined before any antiviral treatment [21–23], we examined five different strategies in two patient groups: those with genotype 1 (G1) and those with genotype non-1 (G non-1, mostly genotype 2/3). We considered only those patients with mild to moderate hepatitis (including bridging fibrosis) but not cirrhosis, because the optimal antiviral treatment of cirrhotic patients is still under clinical evaluation.

1. IFN monotherapy (IFN): reflecting current recommendations [22,24], the viral response is determined after 12 weeks of IFN treatment. Only responders continue antiviral treatment for an additional 36 weeks (IFN 3 MIU sc TIW for 48 weeks, if at 12 weeks HCV RNA [PCR] undetectable).
2. Combination therapy I (Comb I): patients are treated for 24 weeks (IFN 3 MIU sc TIW and

ribavirin 1000/1200 mg orally once daily for 24 weeks).

3. Combination therapy II (Comb II): after 24 weeks of combination therapy, viral response is determined and only responders continue treatment for an additional 24 weeks (IFN 3 MIU sc TIW and ribavirin 1000/1200 mg orally once daily for 48 weeks, if at 24 weeks HCV RNA [PCR] undetectable).
4. Combination therapy III (Comb III): patients are treated for 48 weeks (IFN 3 MIU sc TIW and ribavirin 1000/1200 mg orally once daily for 48 weeks).
5. No treatment: natural history without antiviral treatment.

Patient characteristics

The patient characteristics and the effectiveness of treatment strategies were extracted from a data set of 1445 patients with mild or moderate hepatitis from two randomized trials comparing IFN with IFN-R [13,14]. The mean patient age was 42.2 years (G1, 43.2 years; G non-1, 41.3 years); 34.9% were female; 66.3% had moderate hepatitis; 64.6% of the patients were infected with G1 and 32.0% were infected with genotype G2 or G3.

We defined an SR as viral negativity (HCV RNA negative by PCR, i.e. ≤ 100 copies/ml) 24 weeks after treatment. For our calculations, the SRs shown in Table 1 were applied.

Costs

The study included total direct costs for the year 1998 from a societal perspective, but excluded indirect costs, such as lost productivity. To calculate the present value of future costs, we used a 3% annual discount rate. The cost evaluation followed actual treatment patterns for Switzerland. The costs of complications from HCV (the annual frequency and type of medical care for each disease state) were estimated by a panel of Swiss physicians (two gastroenterologists and three hepatologists). Costs for GP surgery visits and laboratory tests were based on reimbursement tariffs [25], and the costs for drugs were based on current retail prices.

Table 1 Probability of sustained viral response (%)*

| Strategy | Overall | Genotype non-1 | Genotype 1 |
|----------|---------|----------------|------------|
| IFN | 15.0 | 27.5 | 8.3 |
| Comb I | 33.8 | 62.1 | 18.0 |
| Comb II | 40.7 | 61.2 | 29.6 |
| Comb III | 41.6 | 62.4 | 30.2 |

*Data extracted from 1445 patients with mild or moderate hepatitis C treated in two randomized trials [13,14]. IFN, interferon; Comb I, combination therapy I; Comb II, combination therapy II; Comb III, combination therapy III.

Costs of monitoring and antiviral treatment

The costs of treatment reflected current recommendations for Switzerland [23], and included a liver biopsy, HCV RNA testing, genotyping and GP surgery visits with laboratory tests.

Costs of care

The average length of stay per complication was based on the database of the Swiss Hospital Association (VESKA) [26] and on separate evaluations based on a consecutive series of liver transplantations (1995–1997) at the University Hospital, Berne (E.L. Renner, unpublished data). Information on individual cost elements was obtained mainly from VESKA and separate calculations of two large hospitals. The cost of a liver transplantation was based on an analysis of the Swiss hospital institute (SKI) [27]. We updated these data to reflect the current shorter average length of stay [28] and the increased costs of hospital care [29] (Tables 2 and 3). Cost data are comparable to those reported in the USA [9,15,16]. All costs are calculated in euros (mean 1999 exchange rate euro/USD: 1.067).

The marginal CE is expressed as the additional costs per additional quality-adjusted life year (QALY) gained,

discounted with a rate of 3%. Strategies that are dominated (lower costs and higher effectiveness versus other strategies) were excluded from further evaluations. Similarly, strategies were excluded by extended dominance (a mix of other strategies has lower costs and higher effectiveness).

Quality of life

A panel of Swiss physicians (two gastroenterologists and three hepatologists) estimated the quality of life of the health states using a time trade-off technique [30]. Using these estimates, we assigned a utility weight (0 death, 1 perfect health) to each health state, and used the Markov model to calculate QALY (Table 4).

Sensitivity analysis

We tested the sensitivity of our results to the influence of Poynard's favourable response factors [17], varied discount rates, progression rate of cirrhosis and costs within a wide range.

Results

G1 patients had a lower likelihood of sustained response than G non-1 patients, resulting in a lower life expectancy. The lower SR of G1 patients and longer

Table 2 Costs of antiviral treatment (euros)

| Strategy | | Monitoring | Drugs | Total |
|------------------|----------|------------|-------|-------|
| IFN (48 weeks) | | 1934 | 4340 | 6274 |
| IFN-R (24 weeks) | < 75 kg | 1901 | 6631 | 8532 |
| | > 75 kg | 1901 | 7523 | 9424 |
| IFN-R (48 weeks) | < 75 kg | 2271 | 13263 | 15533 |
| | > 75 kg | 2271 | 15045 | 17317 |
| Contraception | 48 weeks | | 64 | 64 |
| | 24 weeks | | 128 | 128 |

IFN, interferon; IFN-R, interferon alpha-2b with ribavirin.

Table 3 Annual costs of care (euros)

| Disease state | Out-patient care | Hospital care | Total |
|---|------------------|---------------|--------|
| Chronic hepatitis (mild/moderate) | 187 | | 187 |
| Compensated cirrhosis | 276 | | 276 |
| Ascites, diuretic-sensitive | 1375 | | 1375 |
| Ascites, refractory | 3011 | 17793 | 20804 |
| Variceal haemorrhage, 1 year | 1605 | 15974 | 17579 |
| Variceal haemorrhage, following years | 1592 | 2965 | 4557 |
| Encephalopathy, 1 year | 3375 | 8896 | 12251 |
| Encephalopathy, following years | 3375 | 8896 | 12251 |
| Hepatocellular carcinoma (no OP), 1 year | 3375 | 8896 | 12251 |
| Hepatocellular carcinoma (no OP), following years | 2925 | | 2925 |
| Hepatocellular carcinoma (PH), 1 year | 3373 | 32685 | 36058 |
| Hepatocellular carcinoma (PH), following years | 2925 | | 2925 |
| Hepatocellular carcinoma (OLT), 1 year | 12496 | 121918 | 134414 |
| Hepatocellular carcinoma (OLT), following years | 10619 | 979 | 11598 |
| OLT, 1 year | 12496 | 113019 | 125515 |
| OLT, following years | 10619 | 979 | 11598 |

OP, operation; PH, partial hepatectomy; OLT, orthotopic liver transplantation.

Table 4 Quality-of-life adjustments (utility weights)

| Disease state | Utility |
|---------------------------------------|---------|
| Chronic hepatitis | 0.9 |
| Compensated cirrhosis | 0.75 |
| Ascites, diuretic-sensitive | 0.5 |
| Ascites, refractory | 0.2 |
| Variceal haemorrhage, 1 year | 0.5 |
| Variceal haemorrhage, following years | 0.6 |
| Encephalopathy | 0.2 |
| Hepatocellular carcinoma | 0.2 |
| OLT, 1 year | 0.7 |
| OLT, following years | 0.8 |
| PH, 1 year (cirrhosis) | 0.4 |
| PH, following years (cirrhosis) | 0.5 |
| IFN | 0.8 |
| IFN-R | 0.7 |

OLT, orthotopic liver transplantation; PH, partial hepatectomy; IFN, interferon; IFN-R, interferon alpha-2b with ribavirin.

duration of antiviral treatment resulted in higher life-time costs compared with G non-1 patients (Table 5).

Genotype 1

The IFN strategy showed a favourable marginal CE (discounted) of 4886 euros (additional costs per QALY gained). Nevertheless, compared with IFN, Comb II should prolong life expectancy by 1.8 years on average at a still favourable CE ratio (discounted) of 7135 euros (additional costs per QALY gained). Treating all G1 patients for 48 weeks (Comb III) rather than stopping treatment in 24-week non-responders (Comb II), however, led to a loss of quality-adjusted life expectancy, as the quality-of-life decrements associated with treatment of all patients for 48 weeks outweighed the long-term quality-of-life benefits obtained in the additional responders (c.f. Table 1). Thus, for patients infected with

G1 virus, Comb II is the most favourable strategy: it should prolong life and be cost effective.

Genotype non-1

Comb I dominates all other strategies by reducing costs and extending quality-adjusted life expectancy. Again, compared with 24 weeks of combination treatment, the quality-of-life decrements of treating all patients for 48 weeks (Comb III) exceeded the additional long-term quality-of-life benefits. Compared with a strategy of no antiviral therapy (natural history) or treating only 24-week responders for 48 weeks (Comb II), Comb I prolonged life and reduced costs. Thus for G non-1 patients, Comb I is the optimal strategy, lengthening life and saving money.

Sensitivity analysis

To assess the sensitivity of our results to Poynard's approach of favourable response factors [17], we tested each strategy (separately for G1 and G non-1 patients) for the effect of the number of favourable response factors present (c.f. Table 6). Regardless of the number of favourable response factors (except genotype) present, our results remained stable, with Comb II being the most cost-effective strategy for patients with G1 and Comb I being most cost effective for G non-1 patients. Therefore, consideration of known response factors, other than genotype, does not increase effectiveness (QALY) or CE of the treatment strategies tested.

We varied the discount rate from 0% to 5%, reduced the histological progression rates to cirrhosis by 33%, and changed long-term disease costs by $\pm 25\%$. In all cases, our strategies remained below 24 960 euros per

Table 5 Results

(a) Genotype 1

| Strategy* | Lifetime discounted 3% costs (euros) | Discounted 3% life expectancy (QALY) | Discounted CE ratio | Lifetime undiscounted costs (euros) | Life expectancy (years) | Quality-adjusted life expectancy (QALY) |
|--------------|--------------------------------------|--------------------------------------|---------------------|-------------------------------------|-------------------------|---|
| No antiviral | 15 143 | 15.32 | | 28 383 | 29.09 | 23.74 |
| IFN | 16 631 | 15.62 | 4886 | 28 852 | 29.80 | 24.51 |
| Comb I | 21 074 | 15.95 | DOM | 32 238 | 30.56 | 25.35 |
| Comb II | 22 467 | 16.44 | 7135 | 32 154 | 31.61 | 26.53 |
| Comb III | 26 268 | 16.39 | DOM | 35 994 | 31.66 | 26.51 |

(b) Non-genotype 1

| Strategy* | Lifetime discounted 3% costs (euros) | Discounted 3% life expectancy (QALY) | Discounted CE ratio | Lifetime undiscounted costs (euros) | Life expectancy (years) | Quality-adjusted life expectancy (QALY) |
|--------------|--------------------------------------|--------------------------------------|---------------------|-------------------------------------|-------------------------|---|
| Comb I | 14 427 | 17.99 | | 19 673 | 34.45 | 29.95 |
| IFN | 14 665 | 16.48 | DOM | 24 304 | 31.52 | 26.51 |
| No antiviral | 15 143 | 15.32 | DOM | 28 383 | 29.09 | 23.74 |
| Comb II | 19 620 | 17.87 | DOM | 25 146 | 34.41 | 29.80 |
| Comb III | 21 533 | 17.88 | DOM | 26 970 | 34.50 | 29.87 |

* Strategies are in order of the rising lifetime costs.

QALY, quality-adjusted life year; CE, marginal cost-effectiveness ratio; IFN, interferon; Comb I, combination therapy I; DOM, dominated by other strategies; Comb II, combination therapy II; Comb III, combination therapy III.

Table 6 Sensitivity analysis of favourable response factors

(a) Genotype 1 with one or two favourable response factors

| Strategy | Life expectancy (years) | Quality-adjusted life years | Cost-effectiveness per discounted quality-adjusted life year 3% |
|--------------|-------------------------|-----------------------------|---|
| No treatment | 26.18 | 21.23 | |
| IFN | 26.31 | 21.33 | DOM |
| Comb I | 26.83 | 21.88 | DOM |
| Comb II | 27.96 | 23.21 | 9235 |
| Comb III | 27.96 | 23.13 | DOM |

(b) Genotype 1 with three or four favourable response factors

| Strategy | Life expectancy (years) | Quality-adjusted life years | Cost-effectiveness per discounted quality-adjusted life year 3% |
|--------------|-------------------------|-----------------------------|---|
| No treatment | 29.56 | 24.24 | |
| IFN | 30.46 | 25.25 | 3049 |
| Comb I | 31.15 | 26.00 | DOM |
| Comb II | 32.25 | 27.24 | 7193 |
| Comb III | 32.01 | 26.89 | DOM |

(c) Genotype non-1 with two or three favourable response factors

| Strategy | Life expectancy (years) | Quality-adjusted life years | Cost-effectiveness per discounted quality-adjusted life year 3% |
|--------------|-------------------------|-----------------------------|---|
| No treatment | 27.65 | 22.46 | DOM |
| IFN | 29.39 | 24.43 | DOM |
| Comb I | 32.63 | 28.29 | Cost-saving* |
| Comb II | 32.11 | 27.58 | DOM |
| Comb III | 32.28 | 27.74 | DOM |

(d) Genotype non-1 with four or five favourable response factors

| Strategy | Life expectancy (years) | Quality-adjusted life years | Cost-effectiveness per discounted quality-adjusted life year 3% |
|--------------|-------------------------|-----------------------------|---|
| No treatment | 32.92 | 26.90 | DOM |
| IFN | 38.21 | 32.78 | |
| Comb I | 41.20 | 36.17 | 190 (vs IFN); cost-saving* |
| Comb II | 41.21 | 36.07 | DOM |
| Comb III | 41.21 | 36.05 | DOM |

*Lower costs than no treatment.

IFN, interferon; DOM: dominated by other strategies; Comb I, combination therapy I; Comb II, combination therapy II; Comb III, combination therapy III.

QALY gained and thus within accepted CE limits (e.g. 31 577 euros per QALY gained for coronary stenting with single-vessel disease [31]; 2371–17 097 euros per life year gained for cholesterol-lowering therapy with a statin [32]).

Discussion

Our study is based on the original data of the two large randomized trials [13,14] comparing the efficacy of IFN and IFN-R for treatment-naïve patients. This allows for a more detailed CE analysis than previous studies [15,33]. We analysed five different strategies separately for both G1 and G non-1. Cirrhotic patients were not included, as the antiviral treatment of cirrhotic patients is still under clinical evaluation. Our data suggest that a combination therapy according to genotype only is the

most cost-effective strategy. G1 patients should be treated for 48 weeks only if a virological response has occurred after 24 weeks of treatment. For G non-1 patients, IFN-R for 24 weeks dominated all other strategies, including no antiviral therapy.

Our results confirm and extend the study by Younossi *et al.* [15]. We showed that for G1 patients the CE is improved substantially by continuing combination therapy for a further 24 weeks in those patients who are virological responders at week 24. Moreover, taking response factors other than genotype into account, as suggested by Poynard *et al.* [17], did not improve the CE (Table 6). Thus, deciding on the length of combination therapy in non-cirrhotic patients based solely on the presence of genotypes non-1 and 1 and, in the case of the latter, stopping treatment if HCV RNA in serum is still detectable after 24 weeks of treatment, seems simple, effective and cost effective.

Effectiveness of therapy was expressed as QALY gained. When quality adjustments were made, quality-of-life decrements associated with 48 weeks of combination therapy for all patients (Comb III) outweighed the long-term quality-of-life benefits in the additional responders. Thus, 24 weeks of combination therapy in G non-1 patients, and 48 weeks of combination therapy in 24-week responders in G1 patients, maximized QALY.

As with any modelling approach, our analysis is limited by the scarce availability of data on the natural history of hepatitis C. Our conclusions, however, remain stable even when varying assumptions over a wide range. Thus, decreasing yearly progression rate to cirrhosis by as much as 33%, increasing/decreasing long-term disease-related costs by as much as 25%, or varying discount rates between 0% and 5% did not affect our conclusion that Comb I for G non-1 and Comb II for G1 are the most favourable treatment strategies.

Collectively, our data demonstrate that IFN-R therapy for non-cirrhotic patients with chronic hepatitis C is most cost effective when genotype (1 versus non-1) and, in G1, virological response at treatment week 24, are taken into account for determining duration of treatment (24 versus 48 weeks).

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