Treatment of hepatitis C : impact on the virus, quality of life and the natural history

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Abstract

Results of treatment for chronic hepatitis C have improved substantially during the last decade. Combination treatment with interferon alpha 3 MU tiw and ribavirin 1000-1200 mg daily during 24 to 48 weeks leads to sustained virologic response (SVR) in approximately 40% of patients, two to three times more than interferon alpha monotherapy. It was considered standard therapy at the EASL Consensus Conference of February 1999. Recently, results have been published on treatment with pegylated interferons alone and in combination with ribavirin. Pegylated interferon treatment leads to almost doubling of SVR rate as compared with standard interferon monotherapy. Combination of pegylated interferon alpha with ribavirin is most promising, leading to a SVR rate of 54 to 56%. It is to be expected that this treatment will become the new standard. Selected patients with genotype 2 or 3 have now a SVR rate of almost 80%. Response to treatment also leads to significant improvement of quality of life and survival, probably by reducing the risk of developing hepatocellular carcinoma. Recent data suggest that early interferon alpha treatment of patients with acute hepatitis C largely prevents thdevelopment of chronicity. (Acta gastroenterol. belg., **2002**, 65, **90-94**).

Key words : Hepatitis C, treatment, interferon, ribavirin, pegylated interferon.

Introduction

Hepatitis C is a major health problem, it is estimated that some 170 million people are infected worldwide of which 5 million in Western Europe (1,2). It is widely accepted that about 85% of infected persons fail to clear the virus. About 20% of patients with chronic hepatitis C develop cirrhosis in 10-20 years and may die of complications of cirrhosis in the absence of liver transplantation. Furthermore, the incidence of hepatocellular carcinoma is 1-4% per year in patients with cirrhosis (2).

Fortunately, the efficacy of therapy of chronic hepatitis C has considerably improved in the last decade.

Therapy response can be categorized as biochemical, virologic or histologic, at the end of treatment or sustained, i.e. 6 months after completion of therapy. In general, 90 to 95% of patients who achieve sustained virologic eradication of serum HCV RNA 6 months after therapy remain free of detectable HCV RNA with normal liver tests and improvement in their liver biopsy when followed for 5 to 10 years (3). The evaluation of this sustained virologic response (SVR) at 6 months post treatment is the primary endpoint of most therapeutic studies on hepatitis C.

Treatment of chronic hepatitis C

Interferon alpha monotherapy

Initially, chronic hepatitis C was treated with interferon alpha monoherapy. A meta-analysis of interferon alpha-2b trials of at least 2 MU tiw for 24 weeks indicate a SVR of 8%. Extended therapy for 12 to 24 months as well as higher dose therapy resulted in increases in SVR (4). Different types of interferon alpha have similar response rates (5-7). The lower rates of virologic response observed in more recent trials as compared to earlier studies is explained by the increased sensitivity of the assays used for the detection of HCV RNA.

Interferon alpha plus ribavirin therapy

Because of limited efficacy, combination treatment with antiviral, immunomodulatory or anti-inflammatory products were studied. Most promising was combination of interferon alpha, 3 MU tiw, with the nucleoside analogue ribavirin, 1000-1200 mg qd. Two large international trials demonstrated that combination therapy was more effective than interferon alpha only (8,9). These studies showed that combination therapy for 24 or 48 weeks resulted in overall SVR rates of 33 and 41% respectively, versus 6 and 16% with interferon alpha alone. Predictors for better response are genotype 2 and 3, low viremia (< 800,000 IU/mL) and absence of cirrhosis (10). Combination treatment is better in all combinations of genotype and viral load, and 24 weeks of combination is sufficient for genotype 2 and 3 irrespective of viral load and also for genotype 1 if viral load is < 800,000 IU/mL (8,9) (Table 1).

The mechanisms responsible for the improved efficacy of interferon in combination with ribavirin are unknown.

Above mentioned results led to the consideration of combination treatment as the treatment of reference for chronic hepatitis C, as stated at the EASL International Consensus Conference on Hepatitis C, held in Paris, February 1999 (2). In the absence of contraindications standard therapy is the combination of interferon alpha

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Table 1. — **Sustained virologic response rates according to HCV genotype and pre-treatment serum HCV RNA level, from the combined trials of McHutchison *et al.* (8) and Poynard *et al.* (9)**

Genotype	HCV RNA (IU/mL)	IFN 48 wk	IFN + RBV 24 wk	IFN + RBV 48 wk
1	≤ 800,000	25%	32%	33%
1	> 800,000	3%	10%	27%
Non-1	≤ 800,000	36%	61%	64%
Non-1	> 800,000	26%	62%	60%

IFN : interferonalpha-2b.
RBV : Ribavirin.

Table 2. — **Absolute and relative contraindications to interferon and ribavirin, according to the EASL Consensus Conference (2)**

Interferon alpha	
Absolute contraindications	Relative contraindications
– present or past psychosis or severe depression – neutropenia and/or thrombocytopenia – organ transplantation except liver – symptomatic heart disease – decompensated cirrhosis – uncontrolled seizures	– uncontrolled diabetes – autoimmune disorders especially thyroiditis
Ribavirin	
Absolute contraindications	Relative contraindications
– end stage renal failure – anemia – hemoglobinopathies – severe heart disease – pregnancy – no reliable method of contraception	– uncontrolled arterial hypertension – old age

and ribavirin. The duration should be 6 months in genotypes 2 and 3, independent of viremia, and in genotype 1 with low viremia (< 800,000 IU/mL). In genotype 1 with high viremia, treatment should last 12 months.

Further analysis of above mentioned trials (8,9) indicated that patients with chronic hepatitis C who have negative HCV RNA after 6 months of treatment with interferon alpha plus ribavirin should continue for another 6 months unless at least 4 favourable factors are present : genotype 2 or 3 ; HCV RNA < 1,300,000 UI/mL ; no or mild fibrosis ; female gender ; age < 40 (11).

The NIH consensus meeting in 1997 stated that treatment should be stopped if no virologic response was achieved after 12 weeks of treatment with interferon alpha monotherapy (12). This rule seems not to hold true for the combination therapy as 7% of patients in the US study (8) who eventually achieved SVR with the combination treatment were HCV RNA positive at week 12, while measuring HCV RNA at week 24 resulted in an error of only 2% of patients. It is therefore common praxis to continue combination therapy for at least six months, and stopping it when HCV RNA is still detectable at that time.

Multiple side effects are common in patients receiving interferon alpha monotherapy or in combination with ribavirin. Most side effects are manageable, but occasional serious side effects occur. The absolute and relative contraindications to interferon and ribavirin according to the EASL Consensus Conference (2) are given in Table 2.

In Belgium, the combination therapy was finally reimbursed from July 1st 2001 on, more than 2 years after the EASL Consensus Conference !

Pegylated interferons

New information on hepatitis C viral kinetics showed that HCV replicates rapidly, and that the antiviral effect of interferon alpha occurs very quickly within the first day. As 48 hours after injection the viral load is reincreasing, the standard schedule of 3 MU tiw may not be the most appropriate (13).

Induction therapy using a daily dose higher than 3 MU induces a more rapid and more complete inhibition of viral replication. However, SVR appears no better than what could be achieved with standard dose interferon therapy (14). Induction dosing of interferon alpha in combination with ribavirin resulted equally in a higher virologic response at the end of the induction period. The effect was lost at the end of therapy and after a 6 months follow-up (15).

Conjugation of interferon alpha with polyethylene glycol (pegylated interferon) increases the half-life and improves the pharmacodynamics (16), allowing one injection per week.

Two molecules have been developed. Peginterferon alpha-2a results from the attachment of a 40 kDa branched polyethylene glycol moiety to the interferon alpha-2a molecule. It is cleared primarily by the liver. Peginterferon alpha-2b is characterized by the attachment of a 12 kDa linear polyethylene glycol moiety to the interferon alpha-2b molecule. Renal elimination accounts for 30% of the clearance.

Two large randomised controlled studies have been performed in naïve chronic hepatitis C patients with pegylated interferon alpha-2a (17) and alpha-2b (18), showing a twofold improvement in efficacy as compared with standard interferon alpha.

In the former study (17), 264 patients received standard interferon alpha-2a at the dose of 6 MU tiw for 12 weeks, then 3 MU tiw for 36 weeks, and 267 patients received 180 µg pegylated interferon alpha-2a qw for 48 weeks. The SVR were 19 and 39% respectively ($p < 0.001$).

In the latter study (18), 1219 naïve patients were included and randomised in 4 groups : one group received standard interferon alpha-2b 3 MU tiw for 48 weeks, and 3 groups received pegylated interferon alpha-2b at a dose of 0.5, 1.0 or 1.5 µg/kg qw for 48 weeks. The SVR were 12 and 25% respectively for standard interferon alpha-2b and the 1.0 µg pegylated interferon alpha-2b group ($p < 0.001$).

The results of these two studies cannot be compared since they were independent studies in different populations. The standard interferon alpha arms were also different.

Pegylated interferon alpha combined with ribavirin

Two large randomized controlled studies have been performed with pegylated interferon alpha in combination with ribavirin (19,20).

The former study (19) included 1530 patients randomized in 3 groups treated for 48 weeks : pegylated interferon alpha-2b 1.5 µg/kg qw and ribavirin 800 mg qd ; pegylated interferon alpha-2b 1.5 µg/kg qw for 4 weeks, then 0.5 µg/kg qw for 44 weeks and ribavirin 1000-1200 mg qd, or standard interferon alpha-2b 3 MU tiw and ribavirin 1000-1200 mg qd. The SVR was higher in the pegylated interferon alpha-2b 1.5 µg group (54%) than in the standard group (47%) ($p = 0.01$). In genotype 1, SVR was 42% versus 33% in respectively the pegylated interferon 1.5 µg group and standard treatment ($p = 0.02$). In genotype 2 or 3, SVR was 82% versus 79% (not significant). A retrospective analysis showed that patients with higher dosages than 1.6 mg/kg ribavirin had a better chance of eliminating the virus, indicating that both pegylated interferon alpha-2b and ribavirin should be given adapted to body weight to maximise response rates.

The latter study (20) included 1121 patients randomized in 3 groups treated for 48 weeks : pegylated interferon alpha-2a 180 µg qw and ribavirin 1000-1200 mg qd, or pegylated interferon alpha-2a and placebo, or standard interferon alpha-2b 3 MU tiw and ribavirin 1000-1200 mg qd. The SVR were 56%, 30% and 45% respectively ($p = 0.001$). SVR was 45% in patients with genotype 1 and 76% in patients with genotype 2 or 3 who were treated with peginterferon alpha-2a and ribavirin.

Further studies must analyze the optimal treatment duration for patients with genotypes 2 and 3.

Side effects seem similar between interferon alpha or pegylated interferon alpha combined with ribavirin.

Future therapies for chronic hepatitis C

Future approaches for therapy of chronic hepatitis C are based on modulation of the host immune response or on specific inhibition of viral replication.

Therapeutic vaccines are currently being explored to enhance humoral and cellular immune responses (21).

Inhibitors of the viral enzymes protease, helicase, polymerase are being developed. It is likely that inhibitors of viral enzymes will be used as part of a combination regimen.

Inhibition of viral replication could also be accomplished by short antisense peptides that specifically bind to the complementary cytosolic mRNA (22).

Effect of treatment of chronic hepatitis C on quality of life

Studies indicate that chronic hepatitis C patients score worse than matched controls on various health-related quality of life scales (23-25). Sustained responders to interferon alpha monotherapy (23,24) or combination therapy with ribavirin (24,25) achieved benefits in their quality of life and work functioning.

Impact of treatment of chronic hepatitis C on the natural history of the disease

Studies from Japan showed that the incidence of hepatocellular carcinoma was lower in interferon treated patients than in untreated controls (26-29). The development of liver tumours was significantly reduced in both sustained and transient responders, but not in nonresponders and in untreated controls (26-29). Interferon therapy was associated with a reduced risk for hepatocellular carcinoma also among patients with sustained normal ALT levels but persistence of serum HCV RNA and those with ALT < twice the upper limit of normal (27). This indicates that not only disappearance of viraemia but also improvement of hepatic necroinflammatory activity influences the rate of liver cancer appearance.

The limited data in Caucasians indicate that the hepatocarcinogenesis rate in untreated patients without preexisting cirrhosis was too low to show the cancer-preventive action of interferon (30).

Follow-up studies from the East and the West indicate an excellent survival (100% probability at 5 years) in sustained responders to interferon (29,31).

Treatment of acute hepatitis C

Whether acquisition was by blood transfusion, needlestick, injecting drug use or mucosal exposure, between 20 and 33% of patients develop symptomatic acute hepatitis C. Once infected, up to 85% of patients will follow a chronic course of disease (32,33). The possibility that hepatitis C may be treated early in its acute phase leading to a reduction in the potential for viral persistence is enticing.

A meta-analysis of randomized controlled trials using interferon alpha 3 MU tiw for 6 to 24 weeks showed that treated patients were more likely to clear the virus and normalize aminotransferase levels than untreated patients (32).

A recent German study treating 44 patients with acute hepatitis C with interferon alpha monotherapy for 24 weeks shows a clearance of HCV RNA in 98% of

cases (34). Similarly, a Belgian study has shown that treatment with interferon alpha at a dosage of 5 MU qd for 2 months gives a SVR in 85% of treated patients (35).

To date there are no published trials using interferon alpha and ribavirin to treat acute infection.

Conclusions

At this moment, standard therapy for chronic hepatitis C is moving from the combination treatment of interferon alpha plus ribavirin (SVR rate of ca 40%) towards combination of pegylated interferon alpha plus ribavirin (SVR rate of 54-56% according to available data). The combination of pegylated interferon alpha-2b plus ribavirin is already registered in the US and in Europe, and available in many European countries, but unfortunately not yet in Belgium. In patients with genotype 2 and 3 SVR rates up to 80% can be achieved with combination treatment, either classical or pegylated interferon alpha plus ribavirin.

Sustained virologic but also biochemical response leads to a reduced risk of development of hepatocellular carcinoma, as demonstrated in studies from Japan, and to improved survival. More prospective studies with longer follow-up will be necessary to evaluate the effect of treatment on the natural history of chronic hepatitis C.

Recent data suggest that early treatment of acute hepatitis C with interferon alpha monotherapy can prevent development of chronic hepatitis C in most patients.

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