REVIEW

The treatment of hepatitis C: history, presence and future

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ABSTRACT

The treatment of chronic hepatitis C has made remarkable progress over the past two decades. For interferon-α monotherapy, sustained virological response rates were between 2 and 9% in genotype 1 and between 16 and 23% in genotypes 2 and 3. By adjusting treatment duration up to 48 weeks for genotype 1 and combining regular interferon-α with ribavirin, sustained response rates could be improved to 28 to 31% in genotype 1 and around 65% in genotypes 2 and 3. Attempts to further increase efficacy included the addition of amantadine without conclusive evidence up till now. With the recent introduction of long-acting pegylated interferon-α in combination with ribavirin, sustained virological response rates of 80% can be obtained in genotypes 2 and 3. However, sustained virological response rates for patients with either genotype 1, nonresponse to prior treatment, cirrhosis or a combination of these characteristics are still less than 50%. In view of results with daily high-dose interferon-α induction in combination with prolongation of treatment duration up to 18 months, such patients might benefit from induction and prolonged PEG-IFN-α treatment and should be treated in an experimental setting.

INTRODUCTION

The Netherlands Journal of Medicine is an offspring of the Folia Medica Neerlandica (1958). The very first publication in this magazine was entitled: 'Viruses as a cause of disease', a topic which has not lost its relevance.[1]
Hepatitis C virus (HCV) is such a cause and currently leading to a global public health problem. Worldwide, 150 to 170 million people are estimated to be chronically infected

with HCV of whom an estimated five million are living in Western Europe. Twenty percent of those chronically infected will eventually develop cirrhosis of the liver and its sequelae within 10 to 20 years in the absence of treatment.[2] Antiviral therapy has now been used for nearly two decades to slow down and prevent this progression. In the past years, the response rate to antiviral therapy has made remarkable progress.

Originally, the response to antiviral therapy in patients with HCV was expressed in terms of biochemical response (normalisation of serum alanine aminotransferase (ALT) levels). However, since the introduction of sensitive PCR assays for the detection of viral RNA, expression in terms of virological response is preferred. Consequently, the success of an antiviral treatment modality is expressed in terms of sustained virological response, defined as a negative result of a sensitive PCR assay for HCV-RNA after a 24-week treatment-free follow-up period. A sustained virological response can be regarded as a surrogate marker for cure of HCV, although it does not completely exclude late virological relapse.

The focus of this review is to summarise past treatments of chronic hepatitis C, to describe the present standard of care and to give recommendations how to improve therapy in the future.

TREATMENT HISTORY: INTERFERON AND RIBAVIRIN

Interferon
In 1986, three years before the identification of the hepatitis C virus by molecular cloning techniques, Hoofnagle *et al.* introduced long-term, 'low-dose' interferon-α (IFN-α) for

the treatment of chronic non-A and non-B hepatitis.[3] Based on these preliminary data, large randomised placebo-controlled trials were performed confirming the effectiveness of IFN-α.[4,5] IFN-α given as a single agent (monotherapy) at a dose of 3 million units (MU) three times a week subcutaneously for 24 weeks induced end of treatment responses (normalisation of ALT levels) in about 50% of patients. However, in about half of the responding patients a relapse was seen within six months after discontinuation of treatment. Further experience indicated that the sustained virological response was even lower; only 6 to 18%. Patients with genotypes 2 and 3 had higher sustained virological responses (16 to 23%) than patients with the predominant genotype 1 (2 to 9%, *table 1*).[6,7] In the years following the introduction of IFN-α, strategies to increase its antiviral activity included the optimisation of dose, treatment duration and the combination with other antiviral agents. One of the first improvements was made by prolonging the treatment duration to 48 weeks. Hereby, post-treatment relapse in HCV-RNA could be reduced significantly, resulting in an increased sustained virological response rate of 7 to 11% in genotype 1 and 29 to 33% in genotype non-1 (*table 1*).[6,8] By therapy prolongation beyond 12 months, the ALT relapse rate in IFN-α monotherapy could be reduced even further.[9,10]

Ribavirin

From all the efforts to increase efficacy, the combination of IFN-α with ribavirin has been the most fruitful. Ribavirin, a nucleoside analogue in use for the treatment of respiratory syncytial virus, lowers ALT levels in many patients with chronic hepatitis C; it has however no significant effect on serum HCV-RNA levels.[11-13] When used in combination with IFN-α, it increases the end of treatment response and reduces post-treatment relapse.[7,14] Large randomised placebo-controlled trials in the USA and other countries have confirmed the enhanced efficacy of combined interferon-ribavirin therapy. Among patients with genotype 1, a sustained virological response was found in 16 to 23% of those treated for six months and in 28 to 31% of patients treated for 12 months. Results in

genotype non-1 were around 65% for both six and 12 months (*table 1*).[6-8] These findings led to the recommendation that patients infected with genotype 1 require a course of 48 weeks of IFN-α plus ribavirin therapy whereas a 24-week combination therapy was sufficient for patients with genotypes 2 and 3.[2]

Amantadine

Amantadine has been used for many years to prevent infection with influenza A virus. Most randomised controlled trials were unable to demonstrate a significant beneficial effect of amantadine-IFN-α over IFN-α monotherapy, largely because of small sample sizes.[15-19] The trials are comparable in design and when the data are pooled – a total of 920 patients have been included – a modest improvement can be demonstrated (*table 2*). Health-related quality-of-life analysis showed an improvement in fatigue and vigour scores in patients receiving combined IFN-α amantadine treatment compared with those treated with IFN-α alone.[15,20] Two trials (one randomised) in IFN-α nonresponders demonstrated significant benefits from the addition of amantadine to the combination of IFN-α and ribavirin.[21,22] The mechanism with respect to this improvement in sustained response remains unclear. Currently a Dutch placebo-controlled multicentre trial on 'triple' therapy in naive patients is in progress in more than 30 hospitals (CIRA study). This study will need a large sample size to demonstrate beneficial effects of amantadine.

High-dose induction and prolonged treatment

Increasing the IFN-α dose or administrating IFN-α daily could be beneficial, because of the high viral replication rate and the short half-life of IFN-α (only hours).[23] Indeed, high-dose IFN-α daily for several weeks, i.e. induction therapy, has been used for years in Japan, resulting in high (more than 80%) initial virological response rates[24] High daily dose IFN-α therapy with or without ribavirin in Western Europe and the USA, however, had no lasting beneficial effect on sustained virological response rates.[25,26] In those early reports, a significant increase of virological

Table 1

Effect of ribavirin and treatment duration

	INTERFERON-αB[#]		INTERFERON-α2B[#] AND RIBAVIRIN[$]	
	24 WEEKS	48 WEEKS	24 WEEKS	48 WEEKS
Genotype 1	2-9[6,7]	7-11[6,8]	16-23[6-8]	28-31[6,8]
Genotype non-1*	16-23[6,7]	29-33[6,8]	50-69[6-8]	64-66[6,8]

Sustained virological response rates in percentages in genotype 1 and genotype non-1 for interferon-α2b (IFN) monotherapy and IFN plus ribavirin for 24 and 48 weeks. Between brackets the literature references from which the results are taken.
*Reflects data on genotypes 2 and 3, data on genotypes 4 to 6 are too limited for inclusion in the table. #Interferon-α2b subcutaneously; dosed 3 million units three times a week. $Ribavirin orally; dosed 1.0 to 1.2 g in two divided doses according to weight.

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Table 2

Effect of amantadine when added to interferon-α

REFERENCE	INTERFERON-α2B	INTERFERON-α2B AND AMANTADINE$	P*
15	13/60 (22%)	6/59 (10%)	0.087
16	17/101 (17%)	29/99 (29%)	0.036
17	15/89 (17%)	21/90 (23%)	0.280
18	15/90 (17%)	22/90 (24%)	0.197
19	17/121 (14%)	25/121 (21%)	0.175
ALL	77/461 (17%)	103/459 (22%)	0.028

Number of patients out of whole group (and percentages between brackets) with sustained virological response for interferon-α2b (IFN) monotherapy and IFN plus amantadine for 48 weeks.
*$Amantadine orally; dosed 200 mg in two divided doses. *Chi-square test.*

response rate (% HCV-RNA negative patients) was found during the high daily dosing period as compared with IFN-α 3 MU three times a week. However, this effect did not result in an increased sustained virological response. This failure to maintain the initial response might be explained by the premature lowering of the IFN-α dose within the first week[27] or due to a short duration of treatment which was stopped after 24 to 26 weeks (24). In a later randomised controlled trial in 373 patients,[28] two experimental induction schedules were compared with a regular schedule of 38 weeks IFN-α 5 MU every other day. In genotype 1 patients, the sustained virological response was nearly twice as high (SVR: 42% versus 27%) when treated with induction therapy (10 MU IFN-α daily for two weeks, followed by 10 MU every other day for 12 weeks, followed by 5 MU every other day for 24 weeks). Sustained virological response rates in the non-1 genotypes varied between 56 and 76% in the three treatment arms but did not differ significantly. These data suggest beneficial effects of high-dose induction and prolonged daily IFN-α dosing in genotype 1 patients in whom success is limited when treated with standard therapy.

In an effort to analyse the above-mentioned treatment strategies combining high-dose induction IFN-α and prolonged daily IFN-α plus ribavirin we performed a meta-analysis on individual treatment data of an exploratory study performed in our centre.[29] In total, 54 consecutive chronic HCV patients selected for unfavourable baseline characteristics associated with therapy resistance such as genotype 1 infection, cirrhosis, previous nonresponse to IFN-α or combinations of these, were treated intensively for 76 weeks. The first 24 patients were treated with a very intensive schedule which resulted in an overall sustained response rate of 67% (95% confidence interval 45 to 84%).[30] In the following patients, attempts were made to decrease morbidity and cost without losing efficacy. However, by shortening the induction period adverse

effects decreased somewhat as did the effectiveness.[27] Thus no clear advantage was found over the original intensive treatment schedule.

The induction phase of 10 MU IFN-α daily for two to four weeks was followed by three to five MU IFN-α injections daily until week 52, and three MU daily or three times a week until week 76. Throughout the study all patients received 1000 to 1200 mg ribavirin.

The overall sustained virological response rate was 57% (95% CI 43 to 71%). Sustained virological response varied between 75 and 83% for patients with one unfavourable characteristic, between 25 and 60% for patients with two unfavourable characteristics, but was only 17% for those with three unfavourable factors. Ten patients had detectable HCV RNA at week 12, in whom treatment was discontinued (19%). Two patients experienced a virological breakthrough (4%) and one patient was HCV RNA negative at 72 weeks but relapsed in the 24 weeks of untreated follow-up (2%). Four patients were not compliant: they stopped in the first four weeks after discharge from hospital. In six patients (11%), therapy was stopped because of adverse effects (hepatic decompensation (n=2), depression (n=2), cardiac symptoms (n=1) and *Staphylococcus* sepsis (n=1)). These data indicate that patients with either genotype 1, cirrhosis or prior nonresponse can have sustained virological response rates approaching those in genotypes 2 and 3 when treated with high-dosed and prolonged IFN-α based therapy. However, in patients with combinations of these unfavourable criteria, sustained virological response rates were low.

TREATMENT TODAY: PEG-INTERFERON-α AND RIBAVIRIN

PEG-interferon-α monotherapy
The covalent attachment of polyethylene glycol (PEG) to IFN-α extends the half-life and duration of therapeutic activity of IFN-α *in-vivo*, allowing less frequent dosing.

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Four randomised controlled trials have compared the efficacy and safety of PEG-IFN-α monotherapy with standard IFN-α monotherapy.[31-34] One of these studies was designed to investigate treatment efficacy and safety in patients with bridging fibrosis or cirrhosis.[32] Administration of PEG-IFN-α once weekly has an increased antiviral effect compared with IFN-α 3 MU three times a week in naive patients resulting in a reduced breakthrough rate and an increased end of treatment and sustained virological response rate. The optimal dose of PEG-IFN-α was found to be 180 µg per week for PEG-IFN-α2a and 1.5 µg/kg body weight for PEG-IFN-α2b. Sustained response rates in genotype 1 were between 12 and 31% for PEG-IFN-α and between 2 and 6% for standard IFN-α. In genotypes 2 and 3 sustained virological response rates were around 50 and 28%, respectively.

PEG-interferon-α and ribavirin
When PEG-IFN-α is combined with ribavirin the sustained response rate is further improved. Sustained virological response rates in genotype non-1 were 78% for six and 77% for 12 months PEG-IFN-α2a plus ribavirin therapy. As with the treatment with regular IFN-α plus ribavirin, there is no benefit in prolonging treatment to 48 weeks in patients with genotypes 2 and 3 (*table 3*). A reduced ribavirin dose of 800 mg daily was found to be as effective as 1000 to 1200 mg daily in patients with genotypes 2

and 3, but the standard dosage of 1000 to 1200 mg yielded better sustained response rates in patients with genotype 1 in whom sustained virological response rates were 42 to 51% (*table 4*). These outcomes are improved over standard IFN-α ribavirin therapy although still about 50% of genotype 1 patients do not respond.[35-37] During treatment, a 2 log or more decrease in viral load in the first 12 weeks is predictive for sustained virological response. Patients who fail to achieve a 2 log decrease in viral load have a limited chance of achieving sustained virological response and should stop therapy.

One of the major differences between the two PEG-IFNs is fixed dosing for PEG-IFN-α2a and dosing according to weight for PEG-IFN-α2b. Trials comparing efficacy and safety of PEG-IFN-α2a to PEG-IFN-α2b with or without ribavirin have not (yet) been conducted. However, both PEG-IFNs have been compared with standard IFN-α and the increased sustained response rates, safety profile and side effects seem similar.

Consensus guidelines
The improvement in treatment results necessitated the need for updating the available guidelines. Two consensus guidelines, both funded from the public sector to assure independence from the pharmaceutical industry, were provided in 2002.[38,39] According to the National Institutes of Health (NIH) and French consensus guidelines all

Table 3
Effect of pegylation of interferon-α

	INTERFERON-α2B# AND RIBAVIRIN¥ 48 WEEKS[35-37]	P-INTERFERON-α2B/B AND RIBAVIRIN¥ 48 WEEKS[35-37]
Genotype 1	33-36%	42$-46%
Genotype non-1*	61-79%	76-82$ %

Sustained virological response rates in genotype 1 and genotype non-1 for interferon-α2b and PEG-interferon-α 2a or PEG-interferon-α2b plus ribavirin for 48 weeks.

*Reflects data on genotypes 2 and 3, data on genotype 4 to 6 are too limited for inclusion in the table. #Interferon-α2b dosed 3 million units three times a week. PEG-interferon-α2a dosed 180 µg per week. PEG-interferon-α2b dosed 1.5 µg/kg body weight per week. ¥Ribavirin orally; dosed 1.0-1.2 g in two divided doses according to weight. $Ribavirin orally: dosed 800 mg/ day in two divided doses.

Table 4
Effect of ribavirin dose and treatment duration[36]

	PEG-INTERFERON-α2A 180 µG PER WEEK			
	RIBAVIRIN 800 MG		RIBAVIRIN 1-1.2 G	
	24 WEEKS	48 WEEKS	24 WEEKS	48 WEEKS
Genotype 1	29%	40%	41%	51%
Genotype 2-3	78%	73%	78%	77%

Sustained virological response rates in genotype 1 and genotypes 2 and 3 for PEG-interferon-α2a ribavirin for 24 and 48 weeks.

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patients with chronic hepatitis C and an increased risk of developing cirrhosis are potential candidates for antiviral therapy. Patients with genotypes 2 and 3 should be treated for 24 weeks. The NIH guidelines state that sustained virological response for patients with genotypes 2 or 3 are similar to PEG-IFN-α and ribavirin or standard IFN-α and ribavirin therapy. Thus standard IFN-α and ribavirin can still be used in treating patients with genotypes 2 or 3. Since low-dosed ribavirin was found to be as effective as 1000 to 1200 mg daily, 24 weeks of treatment and an 800 mg dose of ribavirin is the new standard for patients with genotypes 2 and 3. According to the consensus statements, patients with genotype 1 should be treated with PEG-IFN-α in combination with 1 to 1.2 g ribavirin for 48 weeks.

Currently, much attention is focused on patient and virus characteristics to enable identification of patients who will or will not benefit from treatment. Major pretreatment factors influencing response rates to combination therapy are HCV genotypes and the degree of fibrosis. Viraemic level, age and gender are of less importance in pegylated IFN-α therapy.[7,31,33,35,36,40]
Since genotype 1 is the predominant genotype in many parts of the world and the improved sustained response rate with combined PEG-IFN-α and ribavirin therapy is only about 50%, more effective treatment for this large group is desirable.
Patients with cirrhosis form another group currently in need of better treatment options. In view of the fact that morbidity and mortality of chronic hepatitis C is predominantly in this category of patients it is of note that most of the large trials of the interferon-ribavirin combination as well as those assessing PEG-IFN-α with or without ribavirin contained only a minority of patients with cirrhosis. Responses in cirrhotic patients are generally less than in noncirrhotic patients although treatment with PEG-IFN-α has diminished these differences. Heathcote *et al.* treated 271 patients with bridging fibrosis or cirrhosis with IFN-α2a *versus* two schedules of PEG-IFN-α2a. Sustained response rates of 12% in genotype 1 and 51% in genotype non-1 infection were found.[32]

TREATMENT TOMORROW: FURTHER THERAPEUTIC OPTIONS FOR GENOTYPE 1 AND CIRRHOSIS

As described above, treatment with high-dose induction IFN-α and prolonged daily IFN-α plus ribavirin was successful in the majority of patients selected for treatment-resistant characteristics. Given the increased effectiveness of PEG-IFN-α, a schedule of high-dose PEG-IFN-α combined with ribavirin for a prolonged period might increase response rates. For PEG-IFN-α induction, the optimal PEG-IFN-α dosage has to be determined by measuring both the levels of IFN-α and the antiviral effects *in vivo* during therapy. Currently, a Dutch multi-centre randomised trial (PIT study) comparing PEG-IFN-α induction and prolonged PEG-IFN-α and ribavirin combination treatment with standard therapy in previous nonresponders is underway. Until now, randomised studies comparing PEG-IFN-α induction to standard PEG-IFN-α therapy have not yet been published.
In naive patients, interferon-based treatment strategies can possibly be further tailored to each individual patient according to early response dynamics. By measuring the decline in viral load in each patient in the first weeks of treatment, dose and treatment duration can possibly be optimised.
Completely different forms of medications, the so-called proteinase-inhibitors, are being investigated for their (additional) anti-HCV effect. These drugs can be taken orally and appear highly effective. Phase II and III clinical trials are currently underway; results are pending. Still, it is unlikely that such new therapy will be available for routine clinical use within the next three to five years.

CONCLUSIONS AND RECOMMENDATIONS

In *figure 1* our opinion on how to treat naive patients with chronic hepatitis C is shown.
Treatment is recommended for patients with an increased risk of developing cirrhosis. Therefore patients with F0-1 (no or minor fibrosis) should only be treated when highly motivated after complete information about side effects. Genotype 2 and 3 patients without cirrhosis are optimally treated for 24 weeks with (PEG)-IFN-α in combination with a low dose (800 mg/day) of ribavirin resulting in an 80% sustained response rate. Patients with cirrhosis and geno-types 2 and 3 have a limited chance of sustained response when treated for 24 weeks and should therefore be treated with PEG-IFN-α2a/2b for 48 weeks in combination with 1000 to 1200 mg/day of ribavirin. Genotype 1 patients are preferably treated with PEG-IFN-α2a/2b in combination with 1000 to 1200 mg/day of ribavirin for 48 weeks.
'Difficult to treat patients' with either genotype 1, nonresponse to prior treatment, cirrhosis or a combination of these characteristics who, despite notable advances, still have a chance of less than 50% for sustained virological response might benefit from induction and prolonged PEG-IFN-α treatment and should preferably be treated in an experimental setting. Further research is needed to optimise treatment schedules and to investigate new antiviral drugs in clinical practice; Dutch cooperative studies have the potential to solve some of these outstanding issues.
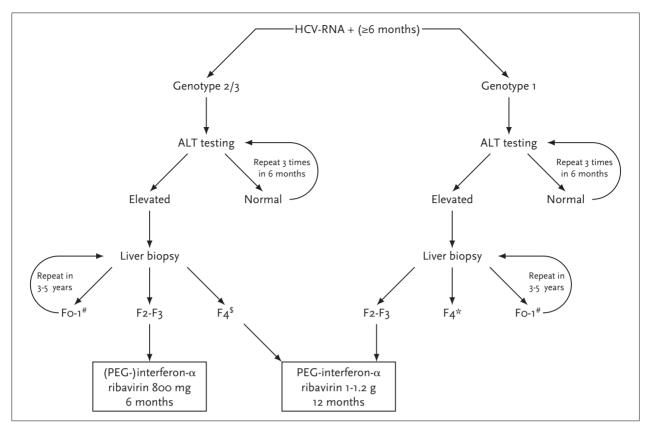
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Figure 1
Individualised approach to treatment of naive patients with chronic hepatitis C according to the authors' interpretation of consensus statements[38,39]

Treatment is recommended for patients with an increased risk of developing cirrhosis, characterised by detectable HCV RNA levels, elevated alanine aminotransferase (ALT) values, a liver biopsy with portal or bridging fibrosis, and at least moderate inflammation and necrosis.
Patients with F0-1 (no or minor fibrosis) have a limited risk of developing cirrhosis and should only be treated when highly motivated after complete information about side effects. Re-evaluation within three to five years is recommended. *Patients with genotype 1 and cirrhosis (F4) should in view of the limited chance of sustained virological response be treated in an experimental setting. $Patients with genotypes 2 or 3 in whom cirrhosis is likely should be treated for one year with PEG-IFN-α and standard-dosed ribavirin.

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