

Expert Opinion

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Treatment of hepatitis C: critical appraisal of the evidence

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Chronic hepatitis C virus infection is currently the most common cause of end stage liver disease worldwide. Although the conclusions of the last National Institutes of Health Consensus Development Conferences on Hepatitis C have recently been published, several important issues remain unanswered. This paper reviews the available data using an evidence-based approach. Current evidence is sufficient to recommend IFN treatment for all patients with acute hepatitis. A later initiation of therapy yields the same likelihood of response as early treatment. A daily induction dose during month 1 is the best treatment option. The current gold standard of efficacy for treatment-naïve patients with chronic hepatitis C is the combination of pegylated IFN and ribavirin. The overall sustained viral response rate to these regimens is 54 – 56% following a 48-week course of therapy. Patients with genotype 1 infection will have a 42 – 51% likelihood of response to 48 weeks of therapy. Those with genotypes 2 or 3 infection will respond to 24 weeks in 78 – 82% of cases. Debate continues regarding the optimal dose and duration of peginterferon (PEG-IFN), not only in patients infected with genotype 2 or 3 but also in those infected with genotype 1. The optimal dose of ribavirin has yet to be determined. Available data show the need to give the highest tolerable doses (1000 – 1200 mg/day) to the difficult-to-treat patients (genotype 1, cirrhotics, obese), although there is a greater likelihood of intolerance. Genotypes 2 and 3 may receive 800 mg/day, which is also the most appropriate lower dose for those patients who require dosage modification for anaemia or other side effects. Tolerability and compliance to therapy are still a problem, as ~ 15 – 20% of patients within trials and > 25% in clinical practice withdraw from therapy. New PEG-IFNs are more effective than conventional IFN in improving liver histology. Monotherapy with PEG-IFN induces a marked reduction in staging in virological sustained responders, and to a lesser degree in relapsers, but provides no benefit to nonresponders after 24 – 48 weeks of treatment. The use of maintenance therapy in virological nonresponders aiming to improve histology should be considered experimental and of unproven benefit. Pooling data from the literature suggests a slight preventive effect of IFN on hepatocellular carcinoma development in patients with HCV-related cirrhosis. The magnitude of this effect is low and the observed benefit may be due to spurious associations. The preventive effect is more evident among sustained responders to IFN.

Keywords: combination treatment, hepatitis C, histological benefit, meta-analysis, pegylated interferon

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1. Background

Hepatitis C virus (HCV) infection is a major health problem worldwide. Chronic hepatitis C is a relevant cause of morbidity and mortality, which could create a significant future public health burden [1-3]. However, only an estimated 20 – 40% of

subjects chronically infected by HCV will eventually develop cirrhosis within 15 – 30 years and die from related complications [4]. These subjects would be the ideal candidates for treatment, but they are not easy to identify in the presymptomatic phase of the disease. Therefore, a universal cure for patients with chronic hepatitis C remains an elusive goal.

Almost 15 years after the first randomised controlled trial (RCT) of IFN therapy in chronic hepatitis C [5], the optimal strategy of treatment of HCV infection remains a matter of debate. Firstly, a substantial proportion (approximately two-thirds) of HCV-infected patients may not be candidates for currently available antiviral treatment for several reasons [6]. Secondly, despite the availability of new and highly effective antiviral treatment, the number of patients who still do not respond to currently available therapies is significant and the new combination regimens of peginterferon (PEG-IFN) and ribavirin are still poorly tolerated [7]. Finally, a major concern is the fact that RCTs of antiviral therapy for chronic hepatitis C have mostly been performed in highly selected population and in patients without advanced fibrosis or cirrhosis. Hence, the transferability of these results to the whole spectrum of subjects with chronic liver disease due to HCV is questionable.

Although the conclusions of the last National Institutes of Health Consensus Development Conferences on Hepatitis C have recently been published [8], several important questions in the management of HCV-infected patients still remain unanswered:

- When and how to treat acute hepatitis C?
- What is the optimal schedule of treatment for chronic hepatitis C?
- What is the histological benefit of antiviral therapy in chronic hepatitis C?
- Is the risk of hepatocellular carcinoma (HCC) truly reduced by antiviral therapy?

In order to answer these relevant issues, this paper will review the available data using an evidence-based approach.

2. When and how to treat acute hepatitis C?

In 2002, the final statement from the National Institutes of Health (NIH) Consensus Conference on the Management of Hepatitis C was that treatment of patients with acute hepatitis C is warranted, and that the minimum dose required for patients with acute hepatitis C to obtain a significant benefit is IFN- α 3 MU three times weekly for at least 12 weeks [9]. However, two unresolved issues remain: when therapy should be started and the optimal schedule of treatment. In order to solve the two issues, the benefit of IFN on acute hepatitis C was evaluated by a recently published meta-analysis [10] that included analysis of 12 controlled trials (445 patients). A large variability in IFN schedule was found with regard to both the total dose which ranged between 3 and 5 – 6 MU, and the length of treatment (range: 4 – 24 weeks). Patients began treatment at different time points from the onset of the dis-

ease, ranging from 15 to 90 days. The mean length of post-treatment follow-up was 16 months (range: 6 – 36 months).

IFN significantly increased viral clearance in all but two trials by Calleri *et al.* and by Fabris *et al.* (Figure 1). The pooled estimate of the sustained virological response (SVR) was statistically significant and clinically relevant (risk difference [RD] +49%; 95% CI = 33 – 65%; $p < 0.00001$; number needed to treat [NNT] = 2). The magnitude of treatment effect was different among studies: the RD of each trial ranged from +5 to +90%. It is possible that this reflects differences in the treatment schedules and in other clinical characteristics of the patients enrolled in the studies. The RD of sustained virological response increased when trials were ordered by increasing total weekly dose, suggesting that induction with a high weekly dose of IFN (≥ 21 MU/week) is the most effective option. Delaying therapy by 60 days after onset of symptoms did not reduce the efficacy of treatment. Overall safety in all trials was good and jaundiced or symptomatic affected patients did not show any severe side effects.

The results of this meta-analysis are subject to several limitations. The available studies are of small size and heterogeneous in methodological quality and design (many of the included studies were nonrandomised controlled trials). The small sample size is justified because it is difficult to enroll patients at diagnosis, either due to the lack of specific diagnostic tests or because the disease is often asymptomatic and rarely recognised outside of surveillance programmes. The studies did not clearly define how the enrolled patients were selected. No study reported whether or not the patients were consecutively enrolled or how many potentially eligible subjects did not enter the trials.

Currently available evidence supports standard IFN monotherapy as treatment for acute hepatitis C. A daily induction dose of at least 21 MU/week during month 1 is the best option, and delaying therapy by 8 – 12 weeks after the onset of disease does not compromise the response to treatment. Assessment of the efficacy safety and costs of PEG-IFN or PEG-IFN and ribavirin combination therapy in acute hepatitis C has not been evaluated so far.

3. What is the optimal schedule for treatment-naive chronic hepatitis C patients?

The current gold standard of efficacy for treatment is the combination of PEG-IFN and ribavirin [11]. The overall SVR rates following the use of these regimens is 54 – 56% after a 48-week course of therapy. Patients with genotype 1 infection will have a 40 – 50% likelihood of response to 48 weeks of therapy [12-19]. Those with genotypes 2 or 3 infection will respond to 24 weeks in 75 – 80% of cases [12-19]. These rates are 5 – 10% higher in all patient groups than those obtained with standard IFN- α and ribavirin. Other conventional predictors of low responsiveness, such as high viral load or advanced liver fibrosis, affect the response to pegylated interferons less than they do with standard IFN [12-19].

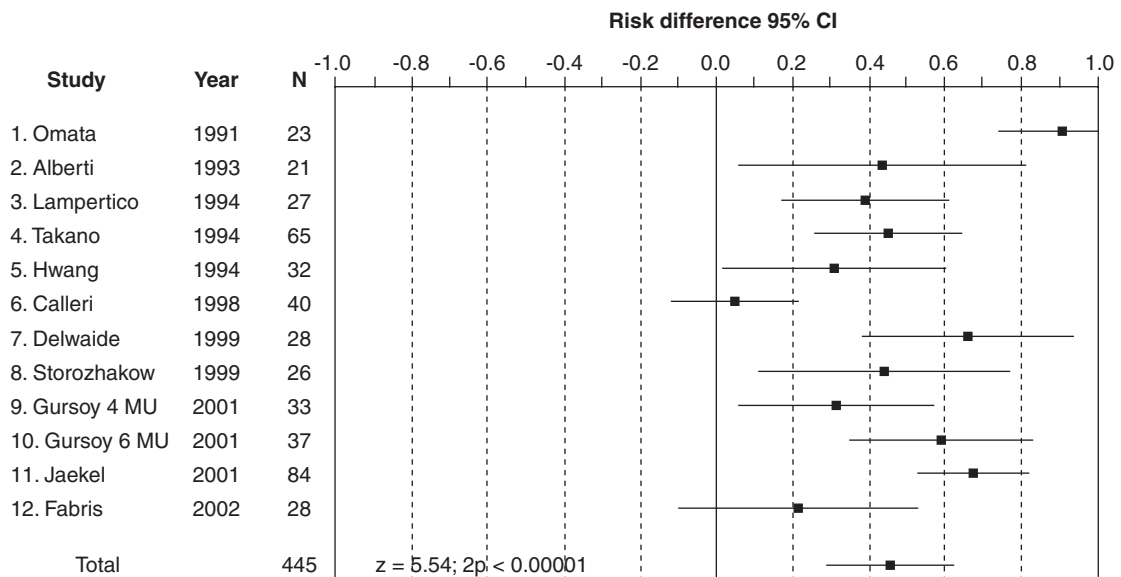


Figure 1. Meta-analysis of 12 controlled trials of standard IFN treatment for acute hepatitis C using a random effects model with sustained virological response as the end point. Risk difference and 95% CI for each study and the pooled estimate of the treatment effect with its confidence interval are plotted. Studies are arranged chronologically (reproduced with permission from Licata A, Di Bona D, Schepis F, Shaied L, Craxi A, Cammà C: *J. Hepatol.* (2003) **39**:1056-1062).

MU: Megaunits; N: Number of patients.

However, these results may not represent the experience of the entire HCV-infected population because most studies have used highly selected patient groups, have been performed in referral centres, and have not reported the screening sample size. Therefore, the extent to which the results of clinical trials in HCV-infected patients apply to the entire HCV-infected population is unknown. Finally, a major issue of concern is the fact that adherence and compliance with therapy, a paramount factor in obtaining high rates of SVR in patients receiving PEG-IFN and ribavirin [7], are still low, and accurate and reliable clinical predictors of compliance are still lacking.

Important questions remain unanswered. What is the optimal treatment regimen for naive patients? Are there any differences in the effectiveness of PEG-IFN treatment between fixed and weight adjusted doses, between standard and low doses of ribavirin and, finally, between patients with different degrees of baseline fibrosis (between cirrhotic and non-cirrhotic patients)?

Therapy of chronic hepatitis C may be improved either by selecting patients with a high likelihood of response or by identifying the optimal treatment regimen of PEG-IFN and ribavirin. Accurate prediction of pretreatment responsiveness to antiviral therapy in the individual patient, however, remains an elusive goal, as the accuracy and reliability of the actual prediction rules are questionable. Many RCTs have been conducted to identify the ideal dose of PEG-IFN, as well as of ribavirin, which would increase the cost-effectiveness of therapy in the individual patient [12-19]. However, the optimal treatment schedule remains ill-defined, as the results of the published studies are inconclusive or conflicting.

An important issue not entirely solved by these studies is whether increased body weight adversely affects response to treatment and whether weight-based dosing should be used even among those who are overweight. It is widely known that chronic hepatitis C runs a more severe course in the obese patient [20-22] and that responsiveness to standard IFN, either alone or in combination with ribavirin [23], is markedly diminished by a high body mass index (BMI). One disputed point in hepatitis C therapy is whether PEG-IFN should be dosed according to body weight or given as a fixed dose. When weight-based dosing is used, it is unclear whether there should be upper and lower limits to the amounts of drug administered. Dose modifications are often required during combination therapy. Most evidence suggests that decreasing the dose of PEG and/or ribavirin does not have a major influence on response rate [7].

A recently published Italian RCT, involving genotype 1 treatment-naïve patients, compared the efficacy and safety of an induction dose of PEG-IFN- α_{2b} 100 $\mu\text{g}/\text{week}$ for 8 weeks followed by a fixed dose of 50 $\mu\text{g}/\text{week}$ for the next 48 weeks, with IFN- α_{2b} 6 MU on alternate days for 48 weeks; both regimens given in combination with a standard dose of ribavirin (1000 – 1200 mg/day) [19]. The study, using a fixed dose of PEG-IFN- α_{2b} , showed in a *post hoc* analysis that there was no significant correlation between the SVR rate and the doses of PEG-IFN- α_{2b} received based on body weight. Interestingly, the SVR rates achieved in a previous study by Manns *et al.* [16], which used a higher dose of PEG-IFN (1.5 $\mu\text{g}/\text{kg}$), paralleled the rates achieved by the Italian RCT in which patients received, on average, PEG-IFN 0.85 $\mu\text{g}/\text{kg}$. This suggests that

the investigators in this earlier study used higher doses of PEG-IFN than is actually necessary. Indeed, we believe that the recommended dose of PEG-IFN- α_{2b} should be redefined by further trials, as the results from one other monotherapy study [14] indicate that 1.0 $\mu\text{g}/\text{kg}/\text{week}$ was the most beneficial dose. Finally, the fact that many patients who were treated with PEG-IFN [12-19] needed a reduction of the dose, yet did not show a reduced SVR, suggests that the currently recommended doses may be unnecessarily high, especially for patients with genotypes 2 and 3.

Weight-based ribavirin dosing is even more difficult to assess. Ribavirin is a drug with a narrow divide between effectiveness and toxicity [24], and works through accumulation in the body. The practice of administering ribavirin 1000 mg/day for patients < 75 kg in weight, and at 1200 mg/day for those above, evolved as a consequence of experience gained in studies of persons with HIV. The pivotal trials of the combination with standard IFN [25,26] adopted this scheme. Recently published RCTs [16-19] have attempted to identify the ideal dose of ribavirin with the aim of maximising the cost-effectiveness of treatment, particularly in persons infected with genotype 1b. The effectiveness of the standard dose of ribavirin (1000 – 1200 mg/day) used in patients with genotype 1 in the Italian RCT [19] is similar to that of the results of two previously reported trials [17,18], in which PEG-IFN- α_{2a} was administered in combination with a standard dose of ribavirin for 48 weeks. These data all provide evidence that a full standard dose of ribavirin, administered over a long course, is particularly needed for genotype 1-infected patients. The observation of Manns *et al.* [16], who reported in a *post hoc* analysis that a dose-response relationship exists between the dose of ribavirin selected on the basis of body weight and the rate of SVR achieved in the low dose (800 mg/day) ribavirin arm of the trial, was not confirmed. This study identified ribavirin > 10.6 mg/kg as the lower end of the optimum dose range. However, the mean body weight dose of ribavirin administered in the low-dose ribavirin arm of the study was 9.7 mg/kg. This suboptimal dose of ribavirin could explain the disappointing rate of SVR observed (30%) in patients with genotype 1 and high viral load in comparison to standard IFN (29%).

Whatever the dose administered, PEG-IFN and ribavirin combination therapy is generally poorly tolerated by patients [12-19]. In the Italian RCT [19], the investigators found that adverse events were the main cause for discontinuation occurring during the first 12 – 24 weeks of treatment, as previously reported [16]. Not surprisingly, changes in fatigue and SF-36 mental and physical summary scores between baseline and 24 weeks of treatment significantly predicted treatment discontinuation [27]. The Italian RCT failed to identify any difference in the baseline characteristics between compliers and non compliers; furthermore, nor did these authors find any relationship between weight-based dosing of both treatments and treatment adherence [19]. Future trials comparing different regimens using quality assurance measures to document

adherence to treatment and the safety profile are still needed. However, even with accurate compliance data, tolerability remains difficult to evaluate because compliance is a non-randomised process within the trial, which interacts with prognostic factors and treatment response [28,29].

Finally, it must be remembered that the optimal regimen in the typical patient with chronic hepatitis C may not be optimal for subgroups of patients (such as those with cirrhosis) or patients with comorbidities (such as HIV infection or renal disease). In the Italian RCT [19], age and degree of fibrosis at biopsy, but not body weight, strongly predicted a SVR to combination therapy with PEG-IFN. These findings are in keeping with other studies, emphasising the importance of age and liver fibrosis in IFN unresponsiveness, and suggest that antiviral treatment should be offered to all eligible patients with genotype 1 as early as possible in the course of their liver disease. Patients with chronic hepatitis C who have contraindications to the use of ribavirin should receive PEG monotherapy and be treated for 48 weeks.

4. What is the histological benefit of antiviral therapy?

Patients with chronic hepatitis C typically undergo liver biopsy to determine the severity of disease and thereby assess the urgency of treatment [30]. The histological findings on biopsy also enable the clinician to evaluate the probability of a response to antiviral therapy. As a tool to evaluate treatment response, however, histology has several significant limitations and sources of bias:

- The histological picture of chronic hepatitis C is mild-to-moderate in most cases; therefore, the relatively small change induced by IFN can be difficult to assess with accuracy and reliability.
- Many factors might influence the interpretation of the histological findings: inconsistency in the definition of pathological features, technical processing of the specimens, sampling variation.
- In most trials, a preliminary assessment of the intra/inter-observer variations in the course of semiquantitative evaluation of histological lesions is not reported. This can be a particularly important source of bias in cooperative studies, or in studies where the biopsy specimens were observed by different pathologists.
- The HAI by the Knodell's method and its modifications are measured on an ordinal scale with non-constant intervals, possibly leading to bias in the cumulative or comparative assessment of data.
- The biopsy specimens reflect a single time-point in a long-term dynamic process and that develops at varying rates and with differing responses to treatment. Accordingly, truly accurate histological assessment of the chronic process requires repeated liver biopsy that obviously cannot be accomplished because of the invasive nature of the procedure.

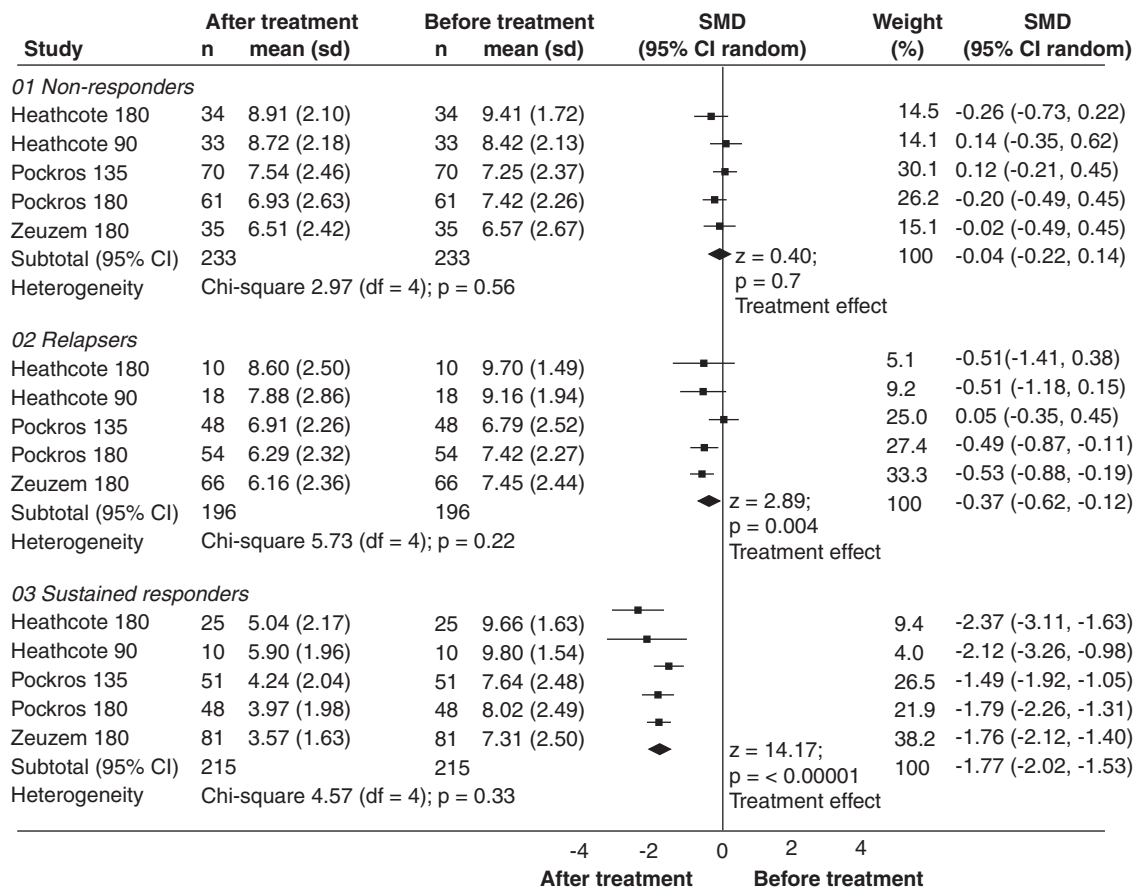


Table 1. Meta-analysis (using a random-effects model) of three RCTs comparing histological score before and after treatment in patients with chronic hepatitis C treated with PEG-IFN-α_{2a}. The standardised mean difference (SMD) and 95% CI for activity, according to virological response to PEG-IFN-α_{2a}, for nonresponders, relapsers and sustained responders are shown. Reproduced with permission from Camma C, Di Bona D, Schepis F *et al.*: *Hepatology* (2004) **39**:333-342.

In 1997, a conventional meta-analysis [31] based on summary data of 17 randomised controlled trials (n = 1223) showed that standard IFN significantly improved liver histology compared with no treatment. Histological improvement was clearly related to antiviral responses. However, drawing firm conclusions based on the results of this conventional meta-analysis is hampered by the considerable heterogeneity in the trials included and by the lack of individual patient data. So far, several large multi-centre RCTs have clearly demonstrated that PEG-IFN produces a significantly greater SVR when compared with standard IFN. Nonetheless, the results of published studies on the effect of these new drugs on liver histology remain inconsistent, and the overall assessment of the treatment effect is difficult to evaluate. To overcome some of the limitations mentioned above and, to improve estimates of effect of size, the results of a recently-published meta-analysis [32] of individual patient data (MIPD) will be summarised.

The primary goals of this MIPD were to determine the differences between PEG-IFN-α_{2a} and IFN-α_{2a} with respect to changes in liver histology, and to identify predictors (clinical, biochemical and virological) of histological improvement.

In this study of 1013 patients who had paired liver biopsies taken before and 24 weeks after the end of the treatment, we showed that interferon treatment improves liver histology and that this effect is more marked with PEG-IFN-α_{2a} than with standard IFN [32]. More specifically, this MIPD has conclusively shown that an impressive reduction in necroinflammatory activity (Table 1), as well as in fibrosis (Table 2), is achieved post-treatment only in virological sustained responders and, to a lesser degree, in relapsers; whereas negligible changes in necroinflammation and no significant changes in fibrosis after treatment occurred in nonresponders. Moreover, these data indicate that patients with a low BMI and a high alanine aminotransferase level at baseline have the highest likelihood of histological improvement. Although the mechanisms responsible for the effect of BMI on liver histology are unknown, a practical recommendation may be to lower body weight in overweight or obese patients before starting therapy. This statement is strengthened by the observation that we found an improvement of fibrosis in the small proportion of nonresponders with the lowest BMI.

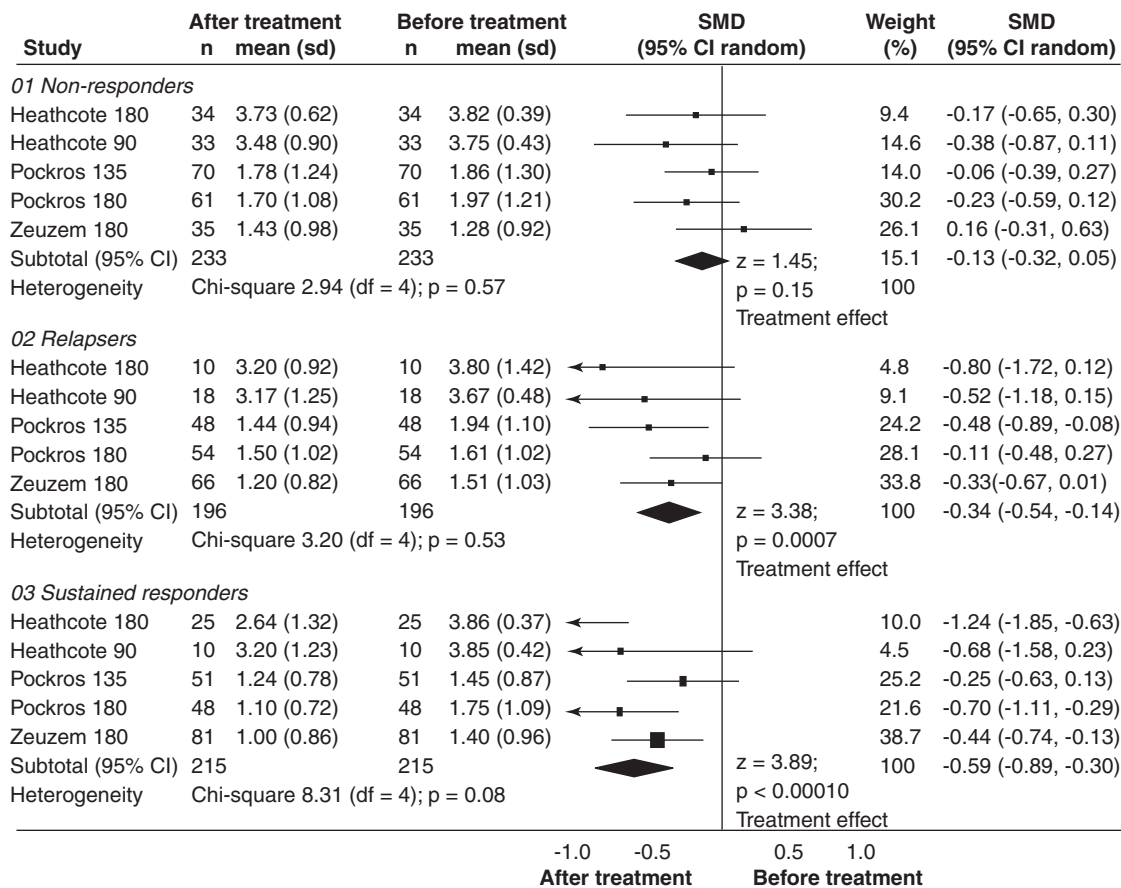


Table 2. Meta-analysis (using a random-effects model) of three RCTs comparing histological score before and after treatment in patients with chronic hepatitis C treated with PEG-IFN- α_{2a} . The standardised mean difference (SMD) and 95% CI for fibrosis, according to virological response to PEG-IFN- α_{2a} , for nonresponders, relapsers and sustained responders are shown. Reproduced with permission from Camma C, Di Bona D, Schepis F et al.: *Hepatology* (2004) **39**:333-342.

It has been suggested that IFN combined with ribavirin slows down the natural progression of fibrosis in virological nonresponders in addition to responders and relapsers [33,34]. This discrepancy with the findings of the MIPD is probably due to the fact that the authors based their analysis on the comparison between the 'fibrosis progression rate per year' before and after treatment [33,34]. There are flaws in using the fibrosis progression rate as a basis for modelling the indication for treatment due to the inaccurate estimations of the duration of infection and the nonlinearity of progression of fibrosis over time. Finally, a complete reversal of fibrosis after treatment was not seen in any of the 198 (19.6%) patients with cirrhosis studied. More specifically, the MIPD provides evidence that the fibrosis score decreases in only 33% of patients with cirrhosis after treatment, and in none of the patients did cirrhosis actually disappear.

There is sufficient information to reach the following conclusions: PEG-IFN- α is more effective than conventional IFN in improving liver histology; monotherapy with PEG-IFN induces a marked reduction in staging in virological sustained responders and to a lesser degree in relapsers after

24 – 48 weeks of treatment but provides no benefit to nonresponders. Therefore, the use of maintenance therapy in virological nonresponders with the aim of improving histology should be considered experimental and of unproven benefit.

5. What is the overall effect of IFN treatment on the prevention of hepatocellular carcinoma in hepatitis C virus-related cirrhosis?

The extensive application of surveillance programmes for early detection of small HCC has increased the opportunity to detect tumours at a subclinical stage when these lesions are potentially responsive to curative treatments [35]. Nonetheless, the 5-year survival rate of patients with small (< 5 cm) HCC undergoing surgical or percutaneous ablation is < 50% [36,37]. This holds true even within intensive screening programmes because of the almost constant presence of underlying cirrhosis and of the high risk of local and distant recurrence, even though treatment had been considered radical. The benefits of orthotopic liver transplantation (OLT) in patients with small HCC are limited by the high rate of tumour progression

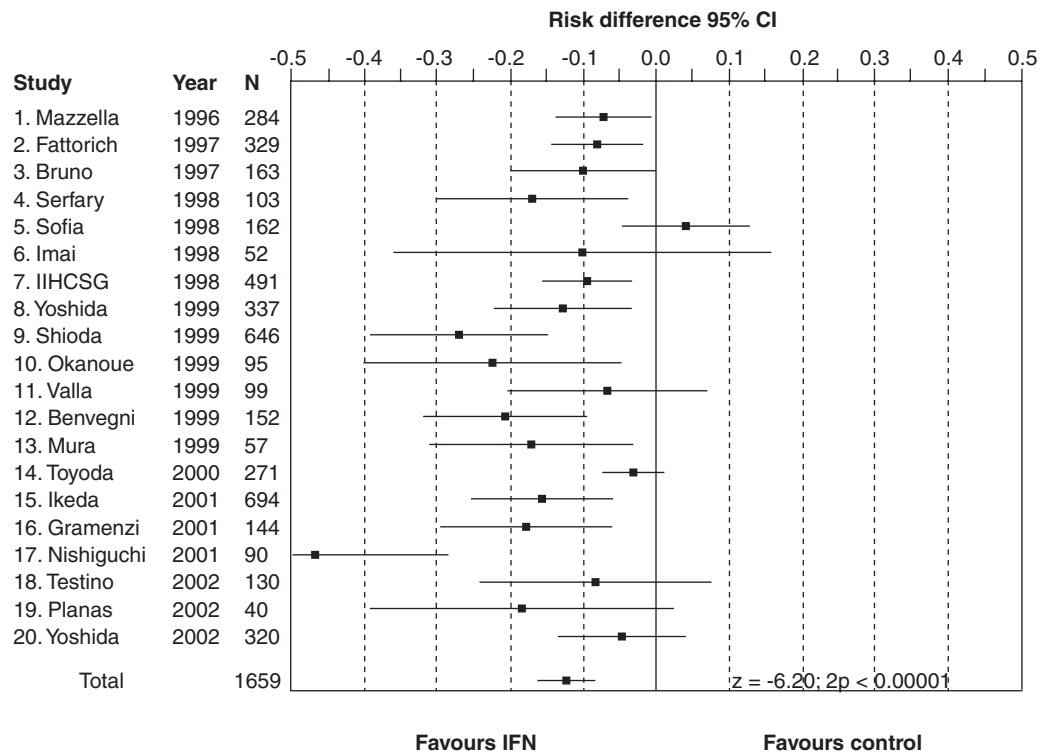


Figure 2. Meta-analysis of the 20 controlled trials of IFN for prevention of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. Risk difference and 95% CI for each study and the pooled estimate of the treatment effect with its confidence interval are plotted on the graph.

and death due to liver disease while still on the waiting list. This applies even to countries with a high number of organs available for OLT [38].

Although early diagnosis and effective treatments are paramount in controlling the death rate of patients with HCC, the importance of cancer chemoprevention has gradually emerged because advanced (i.e., large or locally invasive) HCC is difficult to cure. As the basic mechanism of all cancer development results from accumulation of epigenetic and genetic alterations in cells, the current concept of multistage carcinogenesis has promoted chemoprevention to the stage of a new medical science [39]. Therefore, HCC (chemo)prevention remains a major issue in the long-term management of cirrhotic patients, especially where HCV and overt or occult hepatitis B virus (HBV) infection are the leading cause of chronic liver disease ($\leq 80\%$ in the Mediterranean area) [40].

Chemoprevention may be defined as the use of natural or synthetic agents to reverse, suppress or prevent premalignant lesions from progressing to invasive cancer [41]. A chemoprevention programme for HCC should fulfill the following prerequisites: identification of the risk factors for HCC; determination of the pathogenetic mechanisms of liver carcinogenesis, as well as of the genetic markers that identify the early events in the carcinogenic process and the possible availability of animal tumour models; and evaluation of the

available data from epidemiological and clinical studies on candidate chemopreventive agents.

Chemoprevention of HCC may be classified into three categories:

- Primary: preventing cancer in healthy subjects who are at high risk of exposure to aetiologic factors known to cause chronic liver disease.
- Secondary: preventing cancer in those with premalignant conditions (e.g., HCC prevention in patients with cirrhosis).
- Tertiary: preventing recurrence in patients cured of an initial cancer.

Pooling the available evidence in the setting of secondary chemoprevention and assessing it by meta-analysis, these authors have previously critically reviewed the literature regarding the role and effectiveness of IFN in preventing HCC in patients with HCV-related cirrhosis [42].

It has been argued that long-term suppression of viral replication could reduce hepatocyte turnover and lessen the risk of dysplasia and cancer. In 1995, a small RCT showed that the incidence of HCC in patients with HCV cirrhosis was decreased when compared with untreated controls [43]. In the wake of this study, several controlled trials were performed, mostly in patients with HCV infection. These studies which mostly assessed collected cohorts retrospectively and were of a relatively small size, showed a marked degree of heterogeneity,

thus making it difficult to assess the actual level of benefit obtained by IFN treatment.

Thus, a number of important questions still remain unanswered by the available studies: is the risk of HCC in HCV-related cirrhosis reduced by IFN therapy? If a risk reduction truly exists, does the benefit apply to all patients with HCV-related cirrhosis? Is a sustained response to IFN required to reduce the HCC incidence?

We updated the information gathered in the previous systematic review of the literature [42] in order to evaluate whether newly acquired information supports and even extends the view that IFN reduces the incidence of HCC in patients with viral cirrhosis. The effect of IFN on cancer incidence (three RCTs and 17 nonrandomised controlled trials [NRCTs]: 4659 patients) is shown in **Figure 2**. These studies indicate that in all but one of the 20 evaluable treatment trials, IFN appeared to decrease the HCC rate, with a significant difference being observed in 13. The pooled estimate of the treatment effect was significantly in favour of a preventive effectiveness of IFN (RD: -12.2; 95% CI = -8.4 to -16.1; $p < 0.00001$).

We found remarkable heterogeneity among the studies (chi-square for heterogeneity 69.1 with 19 d.f.; $p < 0.0001$), the most prominent being the difference in magnitude of the treatment effect on the risk of cancer ('quantitative heterogeneity'). Large differences were observed in the baseline risk of HCC among the different trials: the HCC rate in the untreated group ranged from 6.8 to 73%. These two trials represent the extremes of the range of effectiveness: Sofia [44] found no effect of IFN on prevention of HCC, whereas the highest preventative benefit of treatment was observed by Nishiguchi *et al.* [43]. The small sample size of the latter study could be the result of unbalanced randomisation. This is suggested by the low cancer rate in the treated group (26%) compared with the extremely high cancer rate in the control group (73%). The RD of each trial ranged from -33.3 to +3.9%. A pooled analysis excluding both outliers reporting the highest [43] and lowest [44] benefit of IFN treatment once again yielded inconsistent results. We searched for the sources of this variability and found a significant relation between the IFN benefit and HCC rate among untreated patients using both parametric and nonparametric tests (Pearson coefficient: $r = -0.77$; $p = 0.0001$; Spearman rank correlation coefficient: $r = -0.74$; $p = 0.0001$).

As the 20 studies show a marked heterogeneity, subgroup analyses were carried out in relation to the different design

(RCTs versus NRCTs), ethnic origin of patients (European versus Oriental studies), the HCC incidence in the untreated group (rate in controls $\geq 20\%$ versus $< 20\%$) and the type of publication (full papers versus abstracts). Consistent results were only observed when assessing data pooled from RCTs, European reports, studies published as full papers and from trials in which HCC frequency among untreated patients was $< 20\%$ during the follow-up period, ranging between 32 and 76 months.

To test whether the difference in the HCC incidence between treated and untreated groups persisted after adjustment for potentially relevant confounding factors, we performed a logistic regression model including IFN treatment, length of follow-up, cancer rate among untreated patients, design of study (RCTs versus NRCTs), type of publication and ethnic origin of patients. The final model shows that cirrhotic patients treated with IFN have a lower likelihood of developing HCC (OR: 0.28), after adjusting for covariates. Separate subanalyses were performed to evaluate any possible evidence of differential benefit on HCC prevention according to biochemical response to IFN. Analysis by response to treatment showed the pooled RD was -19.1% (95% CI -13.1 to -25.2; $p < 0.00001$) among sustained biochemical responders, without a significant heterogeneity (chi-square for heterogeneity 15.35; $p = 0.053$). The NNT, in studies that included only those with consistent results, was 10. When only patients from these studies who had a sustained response were evaluated, the NNT dropped to 5.2.

The results of this meta-analysis demonstrate that the heterogeneity in the magnitude of the preventative effect of IFN on the risk of cancer is the most impressive feature of these studies. This inconsistency among trials is not surprising because of potential biases in patient selection and in allocation of patients to treatment groups. It is also evident that studies with high HCC rates among controls are more likely to demonstrate a higher estimate of treatment efficacy, whereas those with low rates are more likely to show no benefit.

Regarding HCV cirrhosis, the pooled data suggested a slight preventative effect of IFN on HCC development in patients with HCV cirrhosis. The magnitude of this effect was low, and the observed benefit might be due to spurious associations. The preventative effect was more evident among sustained biochemical responders to IFN, which intrinsically represent a small proportion of all cirrhotic patients.

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