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When and how to treat acute hepatitis C?

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***Background*: Appropriate treatment of acute hepatitis C is still a matter of controversy due to the lack of large controlled trials.**

***Aim*: To assess the effectiveness of interferon as treatment for acute hepatitis C by meta-analysis.**

***Methods*: MEDLINE search (1985–2002) was supplemented with manual searches of reference lists. Studies were included if they were controlled trials comparing interferon to no treatment and if they included patients with either post-transfusion or sporadic acute hepatitis C. Twelve trials were analyzed (414 patients). The outcome assessed was the sustained virological response (SVR) rate (undetectable hepatitis C virus RNA in serum at least 6 months after cessation of therapy).**

***Results*: Interferon significantly increased the SVR (risk difference 49%; 95% confidence interval 32.9–65%) in comparison to no treatment. The risk difference of SVR increased from 5 to 90% when trials were ordered by increasing interferon weekly dose. Delaying therapy by 8–12 weeks after the onset of disease does not compromise the SVR rate.**

***Conclusions*: Current evidence is sufficient to recommend interferon treatment of patients with acute hepatitis C. A later initiation of therapy yields the same likelihood of response as early treatment. A daily induction dose during the 1st month is the best option of treatment.**

***Keywords*: Acute hepatitis C; Interferon; Sustained virological response**

1. Introduction

Over the last 5 years three different meta-analyzes of controlled trials of standard interferon (IFN) as treatment for acute hepatitis C have shown that treating patients with a low dose of standard IFN (3 megaunits [MU] thrice a week) for a short course (12 weeks) is significantly more effective than no treatment in obtaining sustained virological response [1–3]. The substantial overrepresentation of post-transfusion acute hepatitis C in these meta-analyzes (the majority of patients included in the published studies had acquired infection via contaminated blood products) potentially limits their generalizability. Currently, the incidence of post-transfusion acute hepatitis C has fallen markedly, and most cases seen in current practice are acquired by intravenous drug abuse or by non-parenteral and undefined ways [4].

Since the previous meta-analyzes were reported, both a number of uncontrolled studies and an increasing number of controlled trials have been published. However, the results of both controlled and uncontrolled trials remain inconsistent and the overall assessment of treatment effect is difficult to evaluate. In particular, the main limitations of these studies are the small sample size and the high heterogeneity of the enrolled patients due to the asymptomatic course of the disease.

In 2002 the National Institute of Health (NIH) Consensus Conference on the Management of Hepatitis C stated that

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Abbreviations: RCTs, randomized controlled trials; NRCTs, non-randomized controlled trials; IFN, interferon.

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the minimum dose required for patients with acute hepatitis C in order to obtain a significant benefit is 3 MU of α-IFN given three times weekly (TIW) for at least 12 weeks [5]. Although the final statement from the NIH was that treatment of patients with acute hepatitis C is warranted, available data are not sufficient to answer two unresolved issues: when therapy should be started and how patients should be treated [5].

In order to overcome some of the limitations mentioned above as well as increase the relevance of the statistical analysis we performed a meta-analysis of controlled trials on treatment of acute hepatitis C with IFN monotherapy. Our aim was to define the optimal treatment schedule as well as the best time to begin treatment in order to avoid chronic hepatitis C virus (HCV) infection.

2. Materials and methods

2.1. Search strategy and inclusion criteria

The primary source of the studies reviewed was the MEDLINE database (1985–2002), limited to English language literature. The medical subject headings used were acute hepatitis non-A, non-B; acute hepatitis C; interferon; randomized and clinical trials. Reference lists of available review articles and primary studies were also checked to identify other studies not found in the computerized search. Furthermore, we searched the abstracts of the American Association for the Study of the Liver Diseases (1995–2002) and of the European Association for the Study of the Liver (1995–2002).

The potentially relevant papers were initially classified into two subsets. Subset 1 included a total of 12 cohort studies [6–17] that reported data on serum HCV-RNA clearance. The cohort studies of subset 1 were reviewed to assess the overall likelihood of sustained virological response in treated patients [6–8,10,12,13,15–17] and the likelihood of spontaneous HCV RNA clearance in untreated controls [9,11,14], by the Confidence Profile Method using the Fast*Pro software [18–20].

Studies of subset 2 were included in the meta-analysis if they were randomized or non-randomized controlled trials (RCTs and NRCTs), comparing different schedules of standard interferon monotherapy with or without an untreated control group; if they had been published in English as full length papers or abstracts; if they included adult patients with a diagnosis of acute hepatitis C, either post-transfusion or sporadic. Ten of the 26 potentially relevant papers were excluded because the results were published as preliminary reports [21–23] or as abstracts [24–30] before the final article was published. After these ten studies were excluded, 16 controlled trials [31–46], 12 published as a full article [31,33–39,42–44,46] and four as abstracts [32,40,41,45] remained in the meta-analysis.

2.2. Data extraction and outcomes

The trials were first reviewed using a list of predefined, pertinent issues that concerned the characteristics of patients and treatments. Extraction of the data was independently performed by two readers (A.L. and D.D.B.) who compared results and agreed on a consensus.

The following minimal criteria for the diagnosis of acute hepatitis C were present in all studies: (1) increase of ALT level at least 2.5 times above normal, on two separate occasions at least 2 weeks apart; (2) serological exclusion of HAV, HBV, EBV, CMV and HSV; and (3) reliable exclusion of non-viral causes of hepatitis (i.e. hepatotoxins or severe right sided heart failure or autoimmune hepatitis). Exclusion of subjects with pre-existing chronic hepatitis C and/or chronic liver disease was explicitly mentioned in all studies, based on history, physical examinations and biochemistry. In most studies the diagnosis of acute hepatitis C was based on the detection of HCV RNA [31,33–37,39–42,45] in the first serum sample and in five of these [33,36,37,40,42] was confirmed by subsequent seroconvertion from negative to positive anti-HCV, according to international criteria [47].

2.3. Statistical analysis

The outcome assumed as measure of IFN efficacy was the percentage of patients with negative serum HCV RNA after post-treatment follow-up (sustained virological response). The evaluation of therapeutic effectiveness was performed by an intention-to-treat method. When not reported in the trial, the response rate according to intention-to-treat was calculated. In order to combine results from individual trials, we used the proportion of sustained virological responders observed in the treatment and control groups. With these observed proportions of response, the risk differences (RD) were computed for each trial. We calculated the overall RD among the frequencies of the events in both treated and control groups, according to the DerSimonian and Laird random-effects model [48]. In addition to within-study variance, the random-effects model considers heterogeneity among studies. The 95% confidence interval (95% CI) of the RD was also calculated. The number of patients needing treatment (NNT) to obtain one sustained virological response, deriving from the inverse of the risk difference, was also used as a measure of treatment effect [49]. We choose to present the random effect model because we believe that the relevant variation in treatment effects is a consequence of several inter-trial differences.

Since several studies utilized a non-randomized design, we performed the meta-analysis carefully considering the biases that may result because of the lack of randomization [50]. A recommended approach to deal with heterogeneity is sorting the heterogeneous group of studies into subgroups, according to a stratifying variable suspected of causing the inconsistency. We used eleven stratifying variables (RCTs vs. NRCTs, source of infection, studies including patients with baseline ALT $\geq 8/<8$ upper limit of normal, Europeans vs. Orientals, percentage of HCV RNA clearance in untreated patients below/above 15%, long vs. short duration of follow-up, full papers vs. abstracts, high/low dose/week during the 1st month of treatment, starting therapy before/after 60 days, all studies without trials reporting the highest and the lowest therapeutic benefit, studies performed before/after 1995). Finally, we in turn excluded each study to ensure that no study alone would be responsible for the significance of any result (the so-called robust analysis). All our analyzes were computed using a software program.

3. Results

3.1. Cohort studies

To evaluate the effectiveness of interferon treatment on subjects with acute hepatitis C enrolled outside controlled trials, 12 cohort studies [6–17] reporting data on serum HCV RNA clearance of 162 treated [6–8,10,12,13,15–17] and 81 untreated [9,11,14] patients, followed for a mean follow-up of 20 months (range 2–60 months) were analyzed. A total of 243 subjects (25 post-transfusion, 218 sporadic cases) were included. A large variability in interferon schedule was found both in dose (ranging from 3 to 5–6 MU) and in length of treatment (ranging from 4 to 52 weeks).

The overall likelihood of sustained virological response was 70.5% (95% CI 62.6–78.3) for the 162 treated patients, whereas the overall likelihood of achieving a spontaneous serum HCV RNA clearance was 35.3% (95% CI 26.2–44.9) for the 81 untreated controls.

3.2. Meta-analysis

The main features of the sixteen trials included in the analysis are shown in Table 1 [31–46]. A total of

Table 1
Patients characteristics, therapeutic regimens and outcome of each trials included in the meta-analysis

	Study (year of publication)	Type of study	Male (%)	Mean age (years)	Modality of infection (% of sporadic)	Interferon regimens	Dose/week during the 1st month (MU)	Follow-up (months)	Sustained virological response *n* (%)
1	Omata 1991	RCT	36	39	28	β, 3 MU TIW i.v. for 4 weeks	9	36	T 7/11 (63.3) C 1/14 (7.1)
2	Ohnishi 1991	NRCT	60	46	Posttransfusion	β, 3 MU TIW i.v. for 4 weeks	9	24	NR
3	Viladomiu 1992	RCT	60	52	Posttransfusion	α-2b, 3 MU TIW s.c. for 12 weeks	9	12	NR
4	Tassopulos 1993	NRCT	30	48	54	α-2b, 3 MU TIW s.c. for 6 weeks	9	12	NR
5	Li 1993	RCT	22	45	56	α-2b, 3 MU TIW s.c. for 12 weeks	9	12	NR
6	Alberti 1993	NRCT	NR	45	29	α-2a, 6 MU TIW s.c. for 16–24 weeks	18	18	T 8/11 (72.7) C 2/10 (20)
7	Palmovic 1994	NRCT	NR	NR	Posttransfusion	α-r, 3 MU TIW for 24 weeks	9	12	NR
8	Takano 1994	RCT	53	47	29	β, 0.3–6 MU daily i.v. for 4–8 weeks	Na	6	T 32/59 (54.2) C 11/31 (35.5)
9	Hwang 1994	RCT	75	54	Posttransfusion	α-2b, 3 MU TIW s.c. for 12 weeks	9	12	T 9/16 (56.2) C 6/16 (37.5)
10	Lampertico 1994	RCT	14	46	Posttransfusion	α-2b, 3 MU TIW i.m. for 12 weeks	9	18	T 13/22 (59.1) C 6/16 (37.5)
11	Calleri 1998	RCT	85	29	95	β, 3 MU TIW i.m. for 12 weeks	9	22	T 5/20 (25) C 4/20 (20)
12	Delawaide 1999	NRCT	NR	NR	100	α-2b, 5 MU daily s.c. for 8 weeks	35	24	T 11/13 (84.6) C 3/16 (18.7)
13	Storozhakov 1999	NRCT	NR	NR	NR	α 2b, 6 MU TIW s.c. for 18 weeks	18	18	T 7/13 (53.8) C 2/12 (16.6)
14a	Gursoy 1 2001	NRCT	56	38	53	α-2b, 3 MU TIW s.c. for 12 weeks	9	18	T 6/16 (37.5) C 1/17 (5.8)
14b	Gursoy 2 2001	NRCT	56	38	54	α-2b, 6 MU TIW s.c. for 12 weeks	18	18	T 13/20 (65) C 1/17 (5.8)
15	Jaeckel 2001	NRCT	43	36	100	α-2b, 5 MU daily sc for 4 weeks, then 5 MU TIW s.c. for 20 weeks	35	6	T 3/44 (97.7) C 28/40 (70)
16	Fabris 2001	RCT	71	32	NR	α-2a, 3 MU daily TIW s.c for 36 days or 3 MU TIW s.c. for 12 weeks	9 21	6	T 2/6 (33.3) T 3/8 (37.5)

RCT, randomized controlled trials; NRCT, non-randomized controlled trial; NR, not reported; i.v., intravenously; s.c., subcutaneously; i.m., intramusculary; MU, mega units; TIW, three times weekly; T, treated; and C, controls.

640 patients (403 post-transfusion and 237 sporadic cases) were included. Of these 640 patients, 320 were treated and 320 were untreated. The number of patients enrolled in each trial varied greatly, ranging from 14 [36] to 90 [34]. Eight studies were RCTs [25,31–37] and eight were NRCTs [38–45]. We included in the meta-analysis the study of Takano [34], in which six different regimens of IFN were compared, considering the two groups of patients treated with a very low dose of IFN (0.3 MU of IFN-β for 28 or 56 days) as a control group. In fact the rate of response in these two control groups was 21%, which is consistent with the control rate of all other studies. Furthermore in the study by Gursoy [39], two different treatment groups (3 and 6–10 MU) were compared with the same control group. In this trial we performed a comparison with each individual interferon arm and each control group, separately. Finally, in the small trial by Fabris [36], a daily dose of 3 MU of interferon was compared to the same dose administered three times weekly. We combined the results of the two treatment arms of this trial and made a single pairwise comparison with the overall weighted control rate of all the remaining trials.

The criteria for inclusion were uniform in all, but three trials, which included only patients with ALT levels above 8 [39] 10 [42] and 20 [46] times the normal limit. In four trials most patients were jaundiced [40,42,44,46]. HCV RNA was detected in serum by different homemade or commercial polymerase chain reactions.

A large variability in IFN schedule was found either in the individual dose, ranging between 3 MU [31–33,35–39, 43,44,46] and 6 MU [34,40–42,45] or in the length of treatment, ranging between 4 [31,34,43] and 24 weeks [41,42,45]. Patients began treated at different time points from the onset of the disease, ranging from 15 [37] to 89 [42] days. The mean length of post-treatment follow up was 16 months, ranging from 6 [34,36,42] to 36 [31] months.

Nine studies reported the incidence of side effects [33,37–40,42–44,46]. Compliance and overall tolerance of IFN was good. Treated patients experienced side effects as in chronic hepatitis C. No discontinuation of therapy was reported in all trials. IFN was well tolerated also in jaundiced patients [40,42,44,46].

The rate of serum HCV RNA clearance after post-treatment follow-up was reported in 12 studies [31,33–37,39–42,45]. The benefit of IFN on sustained virological response is shown in Fig. 1. IFN significantly increased viral clearance in all, but two trial [36,37]. The highest therapeutic benefit of IFN was observed in the RCT by Omata [31] which is the earliest trial. The pooled estimate of the treatment effect was significant (Risk Difference 49%, 95% CI 33–65, $P < 0.00001$) (NNT = 2). In all the robust analyzes the pooled estimate of the treatment effect was significant.

The magnitude of treatment effect was different among studies. It is possible that this reflects differences in the schedules of treatment. To identify the optimal treatment schedules we performed a meta-analysis of ten trials arranged by increasing weekly dose of IFN administered during the 1st month (Fig. 2). Two trials [31,34] were not included because of the lack of data. The risk difference of sustained virological response increased from 5 to 90% when trials were ordered by increasing weekly dose, suggesting that an induction with a daily induction dose of IFN is the best schedule of treatment.

We found a remarkable heterogeneity among the studies. We performed subgroup analyzes to evaluate whether there was a different effect of treatment in predefined subgroups of trials. Subgroup analyzes were carried out in relation to patients and study characteristics (Table 2). Analysis by rate of HCV RNA clearance in untreated patients below/above 15% showed that the pooled risk difference was 64.5% (95% CI 52.9–76) in studies with a control rate >15%, and 40.1% (95% CI 18.6–61.5%) in studies with a control rate <15%. Analysis by induction schedule showed that the pooled risk difference was 66.6% (95% CI 54.4–78.8) in studies with high weekly dose of interferon and 29.9% (95% CI 16.4–43.3) in those with a low weekly dose of interferon. Analysis by interval from disease onset to therapy showed that the pooled risk difference was 49.9% (95% CI 7.6–93.3) in patients starting treatment within 60 days from disease onset and 45.4% (95% CI 25.4–65.4) in those who received treatment after 60 days from disease onset.

4. Discussion

This meta-analysis of data from 12 controlled trials shows that in acute hepatitis C standard interferon monotherapy significantly improves sustained virological response in comparison to no treatment. The benefit on HCV RNA clearance is large (NNT = 2) and clinically relevant, supporting the decision to treat all patients. It is noteworthy that the same effectiveness was observed in patients in patients enrolled in cohort studies, thus confirming the generalizability of the results obtained in this meta-analysis. Overall, safety in all trials was good, and jaundiced or symptomatic affected-patients did not show any severe side effect. Delaying therapy by 60 days after the onset of symptoms did not reduce the efficacy of treatment. A daily induction dose of standard IFN appears to be highly effective.

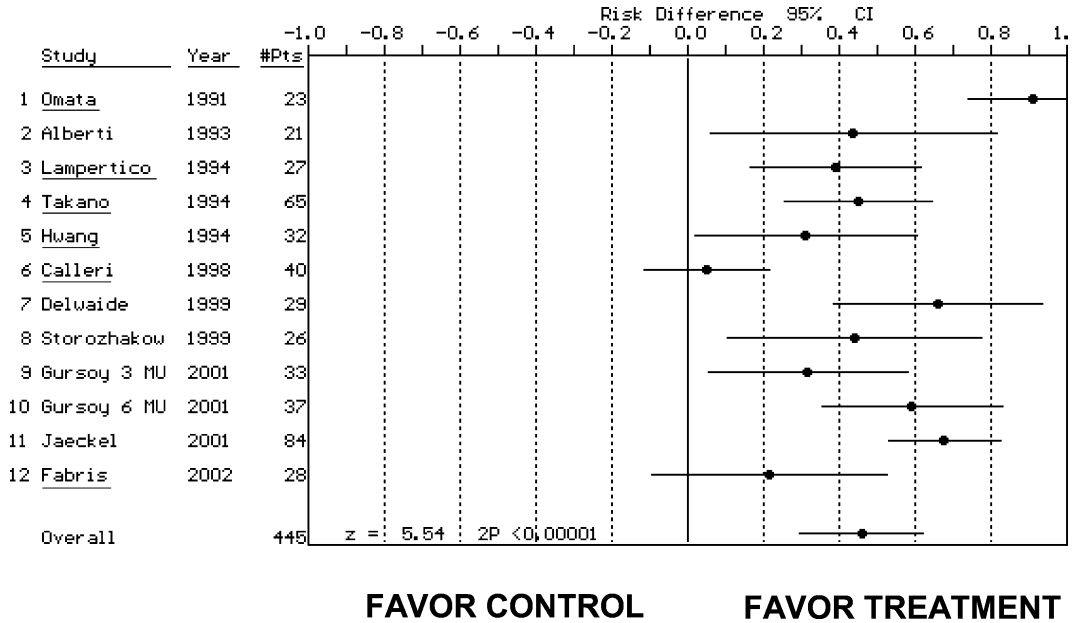

Fig. 1. Meta-analysis of 12 controlled trials [31,33–37,39–42,45] of standard interferon treatment for acute hepatitis C using random-effects model with sustained virological response as endpoint. Risk difference and 95% CI for each study and the pooled estimate of the treatment effect with its Confidence Interval are plotted on the graph. Studies are arranged chronologically based on the year of publication. MU, megaunits. Underlined studies are RCTs.

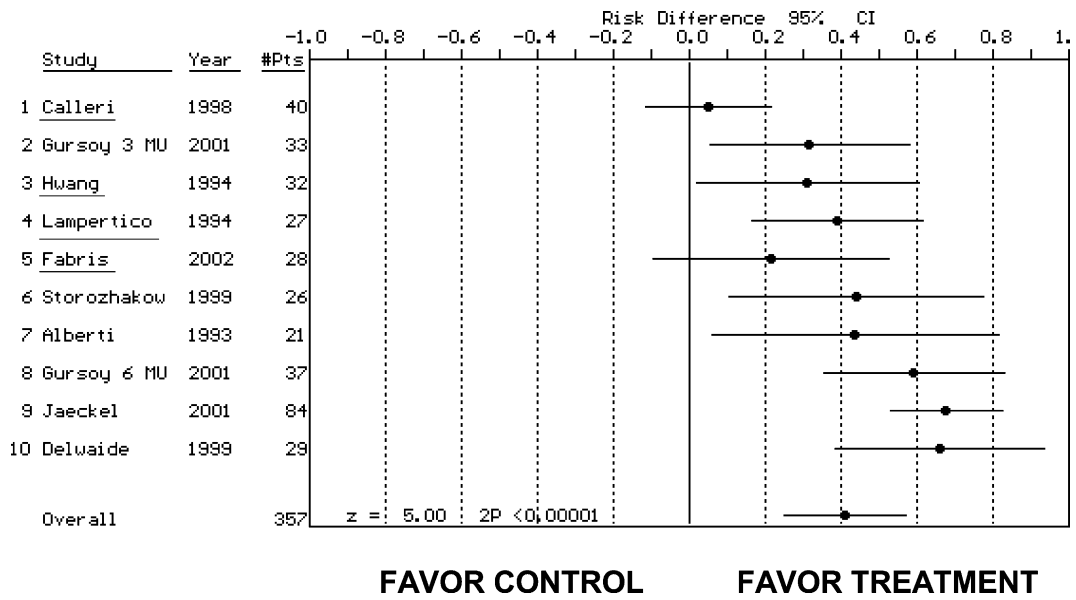

Fig. 2. Meta-analysis of ten controlled trials [33,35–37,39–42,45] of standard interferon treatment for acute hepatitis C using random-effects model with sustained virological response, as end point. Risk difference and 95% CI for each study and the pooled estimate of the treatment effect with its Confidence Interval are plotted on the graph. Studies are arranged based on increasing of weekly dose of IFN administered in the 1st month. MU, megaunits. Underlined studies are RCTs.

Many studies have tried to identify the ideal dose of therapy, as well as factors that would increase the cost-effectiveness of treatment in the individual patient. Since data from controlled trials are still equivocal, the last Consensus Development Conference on hepatitis C did not recommend any regimen of treatment for acute hepatitis C [5]. In the trial by Jaeckel, a regimen of five megaunits of IFN daily for 4 weeks, followed by 5 MU of IFN TIW for 20 weeks achieved a sustained virological response in almost all patients [42]. Similar results were obtained in the study by Delwaide [40], in which a high induction dose was administered. Our meta-analysis provides evidence that treatment with a daily induction dose of standard interferon is the best option for sustained virological response. We believe the available information is inadequate in determining the optimal length of treatment.

Although some authors have suggested that the benefit of interferon monotherapy may be higher in patients infected with HCV genotype other than 1 [6,45] or in patients with low pre-treatment HCV RNA levels [6,33,34], other authors could not confirm these observations [39,40,42,51]. Therefore, a level of accuracy sufficient to predict interferon responsiveness in the individual patient cannot be reached. We observed that the benefit of interferon treatment was higher in the subgroup of trials including symptomatic patients. However, this summary results describe only between-study, not between-patients, variation because they reflect group averages rather than individual data. Thus, caution must be exercised when interpreting results from exploratory analysis.

In this meta-analysis the overall rate of chronicity in untreated patients was very high (ranging from 85% in controlled and 65% in uncontrolled studies), providing a strong rationale for antiviral therapy during the acute phase of the disease. The natural course of acute hepatitis C is poorly defined because the available studies are of small size and are heterogeneous. The small sample size is justified because it is difficult to enrol patients at diagnosis, either for the lack of an accepted serologic definition of acute hepatitis C or because the disease is often asymptomatic, with normal or minimally elevated serum ALT levels, and rarely recognized outside of surveillance programs. Therefore, the best method for detecting an acute HCV infection is to screen high-risk patients for seroconversion from a past negative to a positive test [52].

The key clinical question is whether all patients with acute hepatitis C should immediately receive treatment or whether IFN therapy can be delayed and administered only to the subgroup of patients who might become chronically infected. Santantonio et al. [53], in a prospective long-term study, observed that the chronicity rate was higher in asymptomatic than in symptomatic hepatitis. This prospective study clearly demonstrated that a spontaneous HCV RNA clearance occurs within 8–12 weeks from the onset of the disease. The reported value for spontaneous viral clearance is in keeping with the results of the recently published study by Gerlach [54], showing that patients with acute hepatitis C clear the virus within the first 12 weeks. Finally, Hofer et al. [55] in a small prospective study confirmed that patients with acute icteric hepatitis C have a high rate of spontaneous viral clearance within the 1st month after the onset of symptoms. Moreover, this study showed that viral load declined fast and continuously in symptomatic

Table 2
Sustained virological response in predefinite subgroups of trials

	No. of studies	Rate difference (%)	95% Confidence interval
All studies	12	49.0	33.0–65.0
RCTs	6	45.4	13.8–74.8
NRCTs	6	49.5	31.2–65.3
Source of infection:			
– Posttranfusion	2	36.0	18.2–53.8
– Sporadic	3	45.7	1.3–90.0
– Unknown	7	50.5	29.9–71.2
Studies including patients with high baseline ALT or jaundice	4	56.1	38.8–73.4
Studies including patients with clinically mild acute hepatitis C	8	45.0	21.8–68.2
European studies	9	42.7	25.5–60.0
Oriental studies	3	56.9	20.0–93.6
Studies with a control rate $<15\%$	8	40.1	18.6–61.5
Studies with a control rate $\geq 15\%$	4	64.5	52.9–76.0
Studies with a follow-up <12 months	4	53.1	36.8–69.8
Studies with a follow-up ≥ 12 months	8	43.9	20.6–63.3
Studies published as full paper	8	43.3	22.1–64.5
Studies published as abstract	4	55.8	39.6–72.0
High dose/week during the 1st month	3	66.6	54.4–78.8
Low dose/week during the 1st month	7	29.9	16.4–43.3
Interval from disease onset to therapy:			
– <60 days	4	49.9	7.6–93.3
– >60 days	5	45.4	25.4–65.4
All studies without trials reporting the highest and the lowest therapeutic benefit	10	46.6	35.7–57.5
Studies performed before 1995	5	51.2	26.2–76.3
Studies performed after 1995	7	46.6	24.5–68.7

patients who cleared HCV spontaneously. However, repeated viral load determinations may be not practical in most clinical settings. Drawing firm conclusions based on the results of these uncontrolled studies is hampered by the small sample size and by the selection bias toward symptomatic patients. Thus, an accurate and reliable prediction of chronicity in the individual patient remains an elusive goal, and until now predictors of chronicity across the whole spectrum of patients with acute hepatitis C have not been validated.

Our analysis shows that delaying therapy 2 months after the onset of the disease does not affect the efficacy of treatment. Therefore, from a practical point of view, we suggest that patients be treated 60 days from the onset of symptoms. This strategy avoids the unnecessary treatment of affected patients who would spontaneously recover.

The results of this meta-analysis are subject to some limitations. The included studies did not clearly define how the enrolled patients were selected. Moreover, no study reported whether patients were consecutively enrolled or how many potentially eligible subjects did not enter the trials.

The available evidence support standard interferon monotherapy as treatment for acute hepatitis C. Daily induction dose during the 1st month is the best dose option, and delaying therapy by 8–12 weeks after the onset of disease does not compromise the response to treatment.

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