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Interferon for acute hepatitis C (Review)

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[Intervention Review]

Interferon for acute hepatitis C

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ABSTRACT

Background

Acute hepatitis C virus (HCV) infection progresses to chronicity in the majority of patients. In order to prevent the progression to chronic disease, several studies have assessed interferon in patients with acute hepatitis C.

Objectives

The aim of this review was to assess the efficacy of interferon in acute HCV infection.

Search methods

We searched MEDLINE, the Cochrane Controlled Trials Register, and the abstracts of the American Association for the Study of Liver Diseases (June 2001). We also contacted pharmaceutical companies to obtain unpublished trials.

Selection criteria

Randomised clinical trials comparing interferon with placebo or no treatment, and published as an article, abstract, or letter were selected. No language limitations were used.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data. The following endpoints were analysed: normalization of alanine aminotransferase (ALT) activity at the end of treatment (biochemical ETR); sustained ALT normalization at the end follow-up (biochemical SR); disappearance of serum HCV RNA by polymerase chain reaction assay at the end of treatment (virologic ETR) and at the end of follow-up (virologic SR). Histologic data and adverse events were also recorded. Assessment of drug efficacy used the methods of Peto and Der Simonian and Laird.

Main results

Six randomised trials involving 206 patients with acute hepatitis C met the inclusion criteria. Four trials assessing interferon alfa-2b in 141 patients, all with transfusion-acquired acute hepatitis C, were included. They demonstrated no significant heterogeneity in the outcomes assessed. When compared with no treatment, interferon alfa-2b was associated with an increase in the rates of virologic ETR and SR by 45% (95% CI 31-59%, $P < 0.00001$) and 29% (95% CI 14-44%, $P = 0.0002$), respectively. The virologic ETR was 42% (95% CI: 30-56%) in the interferon alfa-2b group versus 4% (95% CI 0-13%, $P < 0.00001$) in the control group. At the end of follow-up, a virologic SR was seen in

32% (95% CI 21-46%) of interferon-treated patients versus only 4% (95% CI 0-13%, $P = 0.00007$) of controls. Interferon also improved liver biochemistry to a similar extent. The tolerability of therapy, or the impact of interferon alfa-2b on hepatic histology, was not reported. Two trials assessed interferon beta in a total 65 patients. The efficacy of interferon beta could not be assessed, however, due to heterogeneity of these trials.

Authors' conclusions

Interferon alfa is effective in improving biochemical outcomes and achieving sustained virologic clearance in patients with transfusion-acquired acute hepatitis C. The effect on long-term clinical outcomes could not be assessed due to limitations in the current data.

PLAIN LANGUAGE SUMMARY

Interferon alfa improves liver biochemistry and viral clearance in transfusion-acquired acute hepatitis C

Acute hepatitis C is rarely diagnosed because in most cases it is asymptomatic. Treatment of patients with chronic hepatitis C with interferon can achieve viral clearance and improve liver biochemistry and histology. In this review, treatment with interferon alfa in the acute stage of transfusion-acquired hepatitis C infection improved liver biochemistry and enhanced viral clearance compared to the natural history of the disease. We cannot ascertain, however, the effect of interferon on clinical outcomes due to a lack of data. Because of the effect of therapy on biochemical and virologic outcomes, we recommend the treatment of acute hepatitis C with at least interferon alfa at a dosage of three million units thrice weekly for three months. Future trials should focus on the efficacy of combination therapy with ribavirin and pegylated interferons, which have shown superiority to interferon alfa in chronic hepatitis C.

BACKGROUND

Acute HCV infection progresses to chronicity in the majority of patients (Alter 1992; Seeff 2000). In a minority, adverse consequences including hepatocellular carcinoma, the need for liver transplantation, and liver-related mortality occur (Orland 2001; Lauer 2001). Interferon therapy in patients with chronic HCV infection has proven effective in normalizing liver biochemistry, achieving sustained virologic clearance (Poynard 1996), and improving hepatic histology (Camma 1997), as well as health-related quality of life (Ware 1999). Multivariate analysis has shown that a sustained response to interferon is independently predicted by a short duration of infection and the absence of cirrhosis (Pagliaro 1994); both are characteristic of acute HCV infection. In order to prevent the progression of acute HCV infection to chronic hepatitis, several studies have assessed interferon in the acute stage. Although results have generally favoured interferon treatment, a statistically significant effect has been difficult to demonstrate potentially due to small sample sizes. The aim of this Review was to assess the impact of interferon in a large sample of patients with acute HCV infection using pooled data from these studies in a meta-analysis.

OBJECTIVES

The objective of this Review was to assess the efficacy of interferon versus placebo or no treatment in patients with acute HCV infection. The main outcome measure was the sustained disappearance of HCV RNA from the serum.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials (RCTs) comparing interferon with placebo or no treatment, and published as an article, abstract, or letter were included. There were no language limitations.

Types of participants

Only RCTs including patients with acute hepatitis C were included. Acute hepatitis C was defined as: 1) serum aminotransferase levels above twice the upper normal value; 2) seroconversion of antibodies to HCV, or the appearance of HCV RNA in serum between two and 24 weeks after blood inoculation; and 3) exclusion of other causes of liver disease. RCTs involving patients post-liver transplantation, or co-infected with the hepatitis B virus or human immunodeficiency virus were excluded.

Types of interventions

There was no exclusion for type, dose, or duration of interferon therapy. Only RCTs including placebo or no treatment in a control group were included.

Types of outcome measures

In order to be included, at least one of the following outcome measures had to be reported: normalization of alanine aminotransferase (ALT) activity at the end of treatment (biochemical ETR); sustained ALT normalization at the end follow-up (biochemical SR); and disappearance of serum HCV-RNA by polymerase chain reaction assay (PCR) at the end of treatment

(virologic ETR), and at the end of follow-up (virologic SR). Histologic data and adverse events were also recorded.

Search methods for identification of studies

We searched MEDLINE (January 1966 to June 2001), the Cochrane Controlled Trials Register, and did manual searches of reference lists, since we have previously demonstrated that the sensitivity of the MEDLINE search alone is inadequate (Poynard 1985). All publications describing (or which might describe) RCTs of interferon treatment versus placebo or no intervention in acute HCV were obtained using the search strategy developed by the Cochrane Hepato-Biliary Group (see Review Group details for more information). The following terms were included in the electronic search strategy of MEDLINE and the Cochrane Controlled Trials Register: 'acute hepatitis non-A non-B, -C, clinical trials'. Furthermore, we searched the references of published reviews, hand searched the abstracts of the American Association for the Study of Liver Diseases (1995-2000), and contacted pharmaceutical companies to obtain unpublished RCTs.

Data collection and analysis

Meta-analysis was conducted according to a predetermined protocol following the recommendations of Sacks et al. (Sacks 1987). Methodological quality assessment of the trials was performed by two observers independently using a previously validated questionnaire (Poynard 1988). In this questionnaire, 14 items were analysed: description of the primary outcome measure; criteria of inclusion; number of subjects seen and excluded; number of subjects randomised in each group; number of subjects excluded during the follow-up period; blinding of the doctors, patients, and those responsible for the assessment criteria; a priori sample size calculation; method of randomisation and its concealment; analysis and discussion of covariables; statistical tests used; the number of drop outs; and the power of trials with non-significant results. The concealment of allocation, important in reducing bias, was also analysed according to the following scale (Kjaergard 2001): adequate (A), unclear (B), inadequate (C), and not used (D) (see the table 'Characteristics of included studies').

Range of patient characteristics, diagnoses, and treatments

The following items were recorded as potentially useful in assessing clinical heterogeneity between RCTs: mean age, gender ratio, mean duration of hepatitis, mode of infection, HCV genotype, and type of interferon administered (alfa-2a, alfa-2b, beta, etc).

Criteria of combinability

RCTs were combined only if the same type of interferon was investigated, and if at least one of the given outcomes was assessed. For each RCT, the exact drug dosage was given, as well as the duration of treatment.

Selection and data-extraction bias

All RCTs considered for inclusion were analysed independently by two observers (TP, TT, RM, or VL), who conferred with one another in case of disagreement. The decision as to inclusion or exclusion of studies was independent of the study results.

Statistical methods

RevMan 4.1 (Cochrane Collaboration) and NCSS 2000 (Number Cruncher Statistical Systems, Kaysville, Utah) statistical software were used for all analyses. For the biochemical and virologic outcome measures, all analyses were performed according to the

intention-to-treat method, that is, they included all randomised patients and patients without the outcome measure were considered treatment failures. When not explicitly reported in the publication, the response rate according to the intention-to-treat method was recalculated. Because of a high percentage of patients without a post-treatment liver biopsy, the percentage of patients with histological improvement was estimated according to a per-protocol method, that is, after exclusion of missing data which were not considered treatment failures. For each outcome measure, heterogeneity of results between the control groups was assessed using the Peto et al. method (DeMets 1987). Depending on the presence or absence of significant heterogeneity ($P < 0.1$), drug efficacy was assessed using a random effects model (Der Simonian 1986) or a fixed effects model (DeMets 1987). A significance level of 5% was taken as the alpha risk. Each estimate was reported with its 95% confidence interval (CI). Comparisons between strata were performed using weighted risk differences (WRD). Peto odds ratios are reported in Forrest plots 01.01 to 01.05.

RESULTS

Description of studies

SEARCH RESULTS

Eighteen references of interferon therapy in patients with acute hepatitis C were identified. Twelve of these studies were excluded because the trials were uncontrolled ($n = 6$), non-randomised ($n = 3$), or duplicate publications ($n = 3$). The remaining six trials comprised the core group of our meta-analysis, compared with four in our previous review (Poynard 1996).

TRIALS ASSESSING INTERFERON ALFA-2B

A total of four trials, published between 1992 and 1994, were analysed (Viladomiu 1992; Li 1993; Hwang 1994; Lampertico 1994). All of the trials assessed interferon alfa-2b versus an untreated control arm. One of the trials randomised patients to two arms of different interferon doses versus a control arm (Li 1993); the patients receiving interferon in this trial were analysed together. The dose of interferon was three MU in all studies; the frequency of administration ranged from daily (for one week in a single trial) to every other day. The duration of therapy was 12 weeks in all studies. The median duration of follow-up after the end of treatment was 12 months (range nine to 15 months). The mean age of the included patients was reported in three trials (mean 51 years; standard deviation four years). The proportion of males was reported in all of the trials (mean 62%; range 44 to 75%). All of the patients in these trials acquired their HCV infection via contaminated blood products. The duration of infection was specifically reported in three trials (median eight weeks; range seven to 10 weeks). Two trials reported on virologic parameters at study entry; 74% of the patients in these trials were HCV RNA positive. HCV genotype was reported in only one trial; 54% of patients in this trial were genotype 1.

TRIALS ASSESSING INTERFERON BETA

Two trials, published in 1991 and 1998, were analysed (Calleri 1998; Omata 1991). Both of these trials assessed interferon beta at a dosage of three MU daily for five days followed by thrice weekly for three weeks versus an untreated control arm. Follow-up was for 12 months after the end of treatment in both trials. The mean age of the included patients (mean 34 years; standard deviation six years) and the proportion of males (mean 65%; range 44 to 85%) was reported in both trials. A history of blood transfusion was

reported in 5% of patients in one trial versus 80% in the other. In the former trial, 65% of patients gave a history of injection drug use; this was not reported in the other trial. The mean duration of infection was available from neither of the trials, nor was the proportion of HCV genotype 1 infection. HCV RNA positivity at study entry was reported in only one trial; 88% of patients in this trial were HCV RNA positive on entry into the study.

Risk of bias in included studies

The methodological quality of the six included trials was graded according to a previously validated method which generates a score ranging from -2 to 28 (Poynard 1988). The median scored of the trials assessing interferon alfa-2b was 11 (range, seven to 13) and the mean $\pm$ standard deviation was 10.5 $\pm$ 3.0. The median scored of the trials assessing interferon beta was 10 (range, eight to 12) and the mean $\pm$ standard deviation was 10.0 $\pm$ 2.8. Allocation concealment (Table 1) was not described in any of the trials and none of the trials used blinded reviewers in the assessment of outcomes. In all of the trials, data was analysed according to the intention-to-treat method.

Effects of interventions

INTERFERON ALFA-2B (Forrest plots 01.01-01.04)

- Biochemical response

Four trials of interferon alfa-2b in 141 patients with acute HCV infection met the inclusion criteria (Viladomiu 1992; Li 1993; Hwang 1994; Lampertico 1994). There was no significant heterogeneity in any of the outcome measures assessed. Treatment with interferon alfa-2b was associated with an increase of the biochemical ETR and SR rates by 45% (95% CI 31-59%, $P < 0.00001$) and 29% (95% CI 14-44%, $P = 0.0002$), respectively, versus no therapy. The rate of biochemical ETR was 74% (95% CI 63-84%) in the interferon group versus 30% (95% CI 19-42%, $P < 0.00001$) in the control group. At the end of follow-up, a biochemical SR was seen in 54% (95% CI 42-66%) of interferon-treated patients versus only 25% (95% CI 15-37%, $P = 0.0006$) of controls.

- Virological response

Interferon alfa-2b was also associated with an increase in the rates of virologic response, by 40% (95% CI 27-53%, $P < 0.00001$) at the end of treatment and 29% (95% CI 16-43%, $P = 0.00002$) at the end of follow-up, when compared with controls. The rate of virologic ETR was 42% (95% CI 30-56%) in the interferon group versus 4% (95% CI 0-13%, $P < 0.00001$) in the control group. At the end of follow-up, a virologic SR was seen in 32% (95% CI 21-46%) of interferon-treated patients versus only 4% (95% CI 0-13%, $P = 0.00007$) of controls.

Only one trial assessed the impact of pretreatment patient characteristics on the response to interferon treatment. Using a logistic regression model, Hwang et al. (Hwang 1994) found that only the pretreatment serum HCV RNA level independently influenced the response to treatment ($P = 0.035$). Patients with a virologic SR had significantly lower levels of HCV RNA than those patients who did not respond to therapy (median 0.44 molecular equivalents/ml versus 13 molecular equivalents/ml, $P = 0.02$).

- Histological response

The impact of interferon alfa-2b on hepatic histology was assessed in only one trial (Viladomiu 1992). Out of 28 patients enrolled in this trial, liver biopsies at 12 months of follow-up were available in 11

interferon-treated patients and 10 controls. In general, histologic lesions were more severe in control than treated patients, but differences did not reach statistical significance. In particular, chronic active hepatitis was more frequent in the control group (80% versus 46%, not significant [NS]), whereas minimal histologic changes were more frequent in the interferon group (37% versus 20%, NS). The Knodell score, a validated assessment of the degree of necroinflammatory activity in chronic hepatitis (Knodell 1981), was lower in interferon-treated patients than controls (5.0 versus 9.2), but the difference did not reach statistical significance.

- Clinical response

We were unable to identify any data on clinical response in patients randomised to interferon alpha versus placebo/no intervention.

INTERFERON BETA

Two RCTs assessing interferon beta in a total of 65 patients with acute hepatitis C met the inclusion criteria (Omata 1991; Calleri 1998). The results of these studies were heterogeneous and thus, could not be submitted to meta-analysis. Omata et al. (Omata 1991) compared interferon beta three MU intravenously daily for five days followed by three MU thrice weekly for three weeks versus no treatment. Among 11 treated patients, a biochemical ETR was observed in 7 patients (64%, 95% CI 31-89%) versus only 1/14 controls (7%, 95% CI 0-34%, $P = 0.007$). The four patients in the treatment group who failed to normalize their ALT were given a second course of interferon for four weeks (mean total dose 122 MU), and all but one patient achieved a biochemical SR at the end of three years of follow-up. Including these retreated patients, HCV RNA was undetectable during follow-up in ten treated patients (91%, 95% CI 59-100%) versus only one control patient (7%, 95% CI 0-34%, $P = 0.00004$), suggesting a benefit of interferon beta in acute hepatitis C. Calleri et al. (Calleri 1998), on the other hand, found no benefit of interferon beta in patients treated with three MU thrice weekly for four weeks. At the end of a median follow-up of 23 months, 5/20 of the treatment group (25%, 95% CI 9-49%) had normalized their ALT versus 4/18 controls (22%, 95% CI 6-48%, NS). There was also no difference in the rate of virologic response between treated and control patients. At the end of follow-up, HCV RNA remained detectable in 5/8 treated patients (63%, 95% CI 24-91%) and 11/13 untreated patients (85%, 95% CI 55-98%, NS) in whom serum samples were available for HCV RNA testing.

ADVERSE EVENTS (Forrest plot 01.05)

None of the interferon alfa-2b or interferon beta trials reported a comparison of adverse events between interferon-treated patients and controls. The Viladomiu et al. trial (Viladomiu 1992) did report the frequency of dosage reduction and treatment discontinuation; none of the patients in this study required a reduction in interferon dosage or discontinuation of therapy.

DISCUSSION

This overview identified six published RCTs (Omata 1991; Viladomiu 1992; Li 1993; Hwang 1994; Lampertico 1994; Calleri 1998) compared to only four trials in the previous analysis from our group (Poynard 1996). In acute, transfusion-acquired hepatitis C, a three month course of interferon alfa had a favourable effect upon the biochemical response at the end of treatment which was sustained during 12 to 15 months of follow-up. More importantly, there was a major difference in favour of interferon alfa over no treatment for the sustained clearance of HCV RNA from serum, an outcome measure which has proven durable in

chronic HCV infection (Marcellin 1997). Results of studies with interferon beta were heterogeneous; thus, we cannot recommend this treatment for acute HCV infection. Data regarding adverse events of treatment was poorly reported. Thus, no conclusions regarding the tolerability of interferon therapy in acute hepatitis C can be made based on these trials.

The impact of pretreatment characteristics such as age, gender, and genotype, factors known to affect the response to interferon therapy in chronic hepatitis C (Poynard 2000), could not be assessed due to limitations in the available data. A single study suggested, however, that lower pretreatment levels of HCV RNA predicted a favourable response to interferon alfa-2b treatment (Hwang 1994). Similar findings have been reported in untreated patients with acute HCV infection, in whom spontaneous viral clearance is more likely in patients with lower peak viral titers (Villano 1999), and may relate to the evolution of HCV quasi-species (Farci 2000).

An important question to address in assessing the efficacy of interferon in acute hepatitis C is whether or not this treatment improves the long-term outcome of the disease. We have limited information on the impact of treatment on hepatic histology, and no data regarding its effect on long-term clinical outcomes. In a disease which sequelae generally require decades to manifest (Seeff 1997; Seeff 2000), we cannot assume that an earlier clearance of the virus will translate into less end stage liver disease since 'successfully-treated' patients may have spontaneously cleared the virus in the absence of treatment had they been followed for a longer period. Indeed, some evidence suggests that patients with clinically overt acute HCV infection, the minority (< 25%), but those most likely to seek medical attention and thereby receive treatment, are more likely to spontaneously clear their infection (Giuberti 1994; Villano 1999). Alternatively, in the event of viral persistence, these patients may have proven to be 'slow-progressors', and failed to manifest any adverse sequelae of chronic HCV infection, including the requirement for liver transplantation or liver-related death.

Recognizing these unanswered questions, if the goal of the patient with acute hepatitis C and his/her physician is a greater chance of clearance of HCV RNA from the serum during the short-term, we recommend treatment with at least interferon alfa at a dosage of three MU thrice weekly for three months. In view of the durability of virologic response observed in the included trials, as well as those of interferon treatment in chronic hepatitis C (Marcellin 1997), we expect this benefit to be long-lasting in the absence of reinfection. Several practical questions remain, however, which must be studied in future trials. First, the optimal timing for institution of therapy is unclear. In general, the patients in this Review were treated very early in the course of their infection, usually within three months of transfusion once symptoms had arisen. It may be preferable to institute therapy immediately after exposure, for example in healthcare workers with percutaneous injuries, in order to abort potential HCV infection. Although case studies have claimed benefit from post-exposure prophylaxis, large scale studies have not been completed (Orland 2001). Alternatively, later treatment may be preferable in order to avoid unnecessary treatment with expensive and potentially harmful therapy in the group who would have spontaneously cleared the virus (see below). This expectant approach risks, however, missing a window of opportunity in which the response

to treatment appears enhanced. In our meta-analysis, the response to only 12 weeks of interferon monotherapy in patients with acute hepatitis C was similar to that previously observed with 24 weeks of interferon and ribavirin combination therapy in patients with chronic hepatitis C (McHutchison 1998; Poynard 1998). Currently, there is no compelling evidence supporting other doses or durations of interferon monotherapy in acute hepatitis C. Similarly, combination therapy with ribavirin or the use of pegylated interferons has not been studied in acute hepatitis C. However, the major benefit of these medications in achieving a sustained virologic response in chronic hepatitis C in comparison to the 'old' non-pegylated interferon monotherapy regimen (McHutchison 1998; Poynard 1998; Zeuzem 2001) warrants their assessment in the acute setting. Finally, the cost-effectiveness of interferon therapy in acute hepatitis C should be formally evaluated.

We observed a four per cent rate of viral clearance at the end of follow-up in the untreated control group. This is relatively low in comparison with the 25 per cent rate of ALT normalization at this time, as well as existing literature which suggests that 15-25 per cent of patients spontaneously clear the virus (Alter 1992, Seeff 2000). It is possible that prior studies have overestimated the rate of virologic clearance in untreated patients. Alternatively, and perhaps more likely, spontaneous clearance of HCV may occur later in the course of infection, and would be more likely seen on longer follow-up. Indeed, in a study of 43 injection drug users, who seroconverted to HCV-positivity during extended follow-up, Villano et al. reported spontaneous viral clearance in six patients (14%) at a median of 19 months (range 14 to 45 months) after seroconversion (Villano 1999).

Our Review has several weaknesses, particularly the small number of trials and patients included. RCTs are very difficult to perform in acute HCV infection because this condition is rarely clinically identified (Alter 1992). Furthermore, the incidence of post-transfusion hepatitis has declined dramatically since the widespread application of highly sensitive serologic screening tests for HCV (Donahue 1992; Armstrong 2000). Another potential weakness of this Review is the heterogeneity of the included RCTs for such variables as race, timing and method of diagnosis of acute hepatitis C, and type and dosage of interferon studied. When trials assessing interferon alfa-2b were analysed separately, however, all studies individually showed at least a trend towards improved outcomes in the treated patients. Pooling of the data using meta-analysis, these differences became statistically significant. Another possible weakness of this Review is the potential inclusion of patients with chronic hepatitis C in the absence of pre-transfusion HCV RNA testing in all patients. This possibility is effectively ruled

out, however, by the 25 per cent rate of sustained biochemical response observed in the control group, a rate which has not been duplicated in previous trials in chronic hepatitis C patients (Davis 1989; Thevenot 2001).

Finally, our Review has a substantial overrepresentation of transfusion-acquired acute hepatitis C which potentially limits its generalizability. In fact, in the trials assessing interferon alfa-2b, all of the patients acquired HCV infection via contaminated blood products. As mentioned previously, the incidence of post-transfusion hepatitis C has fallen markedly such that the majority of cases seen in current clinical practice are acquired via injection drug use, occupationally, or sporadically. These patients, particularly intravenous drug abusers, may be less likely than those with transfusion-acquired acute hepatitis C to seek medical attention and receive treatment in the event of an acute icteric illness. Furthermore, the natural history of HCV infection may be different in these patients (Seeff 1997; Poynard 2001), and they may respond differently to interferon treatment in the setting of acute infection. These questions can only be answered by future trials.

AUTHORS' CONCLUSIONS

Implications for practice

In conclusion, this Review confirms the efficacy of interferon alfa on biochemical and virologic outcomes in transfusion-acquired acute hepatitis C. No data are available on the long-term efficacy of interferon alfa on the outcomes of this disease, nor the response in patients with acute hepatitis C acquired via other means.

Implications for research

In the future, the combination of ribavirin with interferon, including the newer pegylated formulations, as well as the optimal timing, doses, and duration of therapy, should be tested in the setting of acute hepatitis C. Response rates in patients with acute hepatitis C acquired via means other than transfusion should also be assessed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Calleri 1998

Methods	Randomisation: yes Blinding: no Intention to treat: yes Methodological score: 8
Participants	- Patients with acute hepatitis C - n = 40 - Arms (IFN/C): 20/20 - RNA + at entry: no data available (NDA) - Excluded: 0/0 - Mean age (y): 29/29 - Male (%): 85/85 - Transfusion (%): 5/5 - Drug abuse (%): 65/65 - Genotype: NDA - Mean disease duration (wk): NDA

Interferon for acute hepatitis C (Review)

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Calleri 1998 (Continued)

Interventions	- Schedule: Control: no intervention Experimental: IFN beta 3 MU/day x 5 d; 3 MU tiw x 3 wk -Follow-up (F/U): 22 mo	
Outcomes	- Biochemical ETR and SR	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hwang 1994

Methods	Randomisation: yes Blinding: no Intention to treat: yes Methodological score: 13	
Participants	<ul style="list-style-type: none">- Patients with acute hepatitis C- n = 33- Arms (IFN/C): 16/17- RNA + at entry: 16/17- Excluded: 0/1- Mean age (y): 53/55- Male (%): 75/71- Transfusion (%): 100/100- Drug abuse (%): 0/0- Genotype: G1 54%, G2 30%, Other 15%- Mean disease duration (wk): 9/10	
Interventions	<ul style="list-style-type: none">- Schedule: Control: no intervention Experimental: IFN alpha-2b 3 MU tiw x 3 mo-F/U: 12 mo	
Outcomes	<ul style="list-style-type: none">- Biochemical ETR and SR- Virologic ETR and SR	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lampertico 1994

Methods	Randomisation: yes Blinding: no	
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Interferon for acute hepatitis C (Review)

Lampertico 1994 (Continued)

Intention to treat: no Methodological score: 13

Participants	<ul style="list-style-type: none"> - Patients with acute hepatitis C - n = 48 - Arms (IFN/C): 27/21 - RNA + at entry: 18/9 - Excluded: 1/2 - Mean age (y): 49/44 - Male (%): 65/47 - Transfusion (%): 100/100 - Drug abuse (%): 0/0 - Genotype: NDA - Mean disease duration (wk): 7/9
Interventions	<ul style="list-style-type: none"> - Schedule: Control: no intervention Experimental: IFN alpha-2b 3 MU tiw x 3 mo - F/U: 15 mo
Outcomes	<ul style="list-style-type: none"> - Biochemical ETR and SR - Virologic ETR and SR
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Li 1993

Methods	Randomisation: yes Blinding: no Intention to treat: yes Methodological score: 9
Participants	<ul style="list-style-type: none"> - Patients with acute hepatitis C - n = 32 - Arms (IFN/IFN/C) : 8/8/16 - RNA + at entry: NDA - Excluded: 5 (IFN/IFN) / 2 - Mean age (y): NDA - Male (%): 44 (IFN/IFN) / 60 - Transfusion (%): 100/100/100 - Drug abuse (%): 0/0/0 - Genotype: NDA - Mean disease duration (mo): 3-6
Interventions	<ul style="list-style-type: none"> - Schedule: Control: no intervention Experimental: - Group A: IFN alpha-2b 3 MU/d x 1 wk; 3 MU/2d x 11 wk - Group B: IFN alpha-2b 3 MU/2d x 12 wk - F/U: 12 mo
Outcomes	<ul style="list-style-type: none"> - Biochemical ETR and SR - Virologic ETR and SR

Interferon for acute hepatitis C (Review)

Li 1993 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Omata 1991

Methods	Randomisation: yes Blinding: no Intention to treat: yes Methodological score: 12
Participants	- Patients with acute hepatitis C - n = 25 - Arms (IFN/C): 11/14 - RNA + at entry: 10/12 - Excluded: 0/0 - Mean age (y): 40/38 - Male (%): 44/50 - Transfusion (%): 88/71 - Drug abuse (%): NDA - Genotype: NDA - Mean disease duration: NDA
Interventions	- Schedule: Control: no intervention Experimental: IFN beta 3 MU/d x 5 days; 3 MU tiw x 3 wk - F/U: 12 mo
Outcomes	- Biochemical ETR - Virologic ETR

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Viladomiu 1992

Methods	Randomisation: yes Blinding: no Intention to treat: yes Methodological score: 7
Participants	- Patients with acute hepatitis C - n = 28 - Arms (IFN/C): 15/13 - RNA + at entry: NDA - Excluded: 0/0 - Mean age (y): 54/51

Interferon for acute hepatitis C (Review)

Viladomiu 1992 (Continued)

- Male (%): 60/70
- Transfusion (%): 100/100
- Drug abuse (%) : 0/0
- Genotype: NDA
- Mean disease duration (wk): 7/7

Interventions	<ul style="list-style-type: none"> - Schedule: Control: no intervention Experimental: IFN alpha-2b 3 MU tiw x 3 mo - F/U: 9 mo
Outcomes	<ul style="list-style-type: none"> - Biochemical ETR and SR - Liver histology - Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

C: control
IFN: interferon
NDA: no data available.
ETR: end of treatment response.
SR: sustained response.
wk: weeks
mo: months
y: years
MU: million units
tiw: three times weekly

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alberti 1994	Controlled, but non-randomised trial.
Colombo 1993	Duplicate publication (Lampertico 1994).
Fukui 1994	No untreated control group.
Genesca 1992	Duplicate publication (Viladomiu 1992).
Lee 1996	No untreated control group.
Ohnishi 1989	No untreated control group.
Ohnishi 1991	Controlled, but non-randomised trial.
Omata 1994	Duplicate publication (Omata 1991).
Palmovic 1994	No untreated control group.

Interferon for acute hepatitis C (Review)

Study	Reason for exclusion
Takano 1994	No untreated control group.
Tassopoulos 1993	Controlled, but non-randomised trial.
Vogel 1996	No untreated control group.

DATA AND ANALYSES

Comparison 1. Interferon alfa-2b versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Biochemical ETR	4	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.87 [3.05, 11.33]
2 Biochemical SR	4	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.23 [1.66, 6.30]
3 Virologic ETR	3	113	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.98 [4.44, 27.15]
4 Virologic SR	3	113	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.80 [2.64, 17.54]
5 Adverse events	1	56	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.1 Dosage reduction	1	28	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Treatment discontinuation	1	28	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Interferon alfa-2b versus control, Outcome 1 Biochemical ETR.

Analysis 1.2. Comparison 1 Interferon alfa-2b versus control, Outcome 2 Biochemical SR.

Analysis 1.3. Comparison 1 Interferon alfa-2b versus control, Outcome 3 Virologic ETR.

Analysis 1.4. Comparison 1 Interferon alfa-2b versus control, Outcome 4 Virologic SR.

Analysis 1.5. Comparison 1 Interferon alfa-2b versus control, Outcome 5 Adverse events.

Study or subgroup	Interferon n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.5.1 Dosage reduction					
Viladomiu 1992	0/15	0/13			Not estimable
Subtotal (95% CI)	15	13			Not estimable
Total events: 0 (Interferon), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.5.2 Treatment discontinuation					
Viladomiu 1992	0/15	0/13			Not estimable
Subtotal (95% CI)	15	13			Not estimable
Total events: 0 (Interferon), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	30	26			Not estimable
Total events: 0 (Interferon), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					
			Favours interferon 0.1 0.2 0.5 1 2 5 10 Favours control		

ADDITIONAL TABLES

Table 1. Grading of the quality of allocation concealment

GRADE	ALLOCATION CONCEALMENT
A	Adequate: central randomisation, sealed envelopes, or similar.
B	Unclear: not described.
C	Inadequate: open table of random numbers or similar.
D	Not performed: no attempt was made to conceal allocation.

WHAT'S NEW

Date	Event	Description
9 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

TP, TT, CR, PM, VL, PO, JPZ wrote the first draft of the protocol and the review. TP, TT, and VL performed the literature searches, and participated in the selection of trials and data extraction. TP and TT performed the statistical analyses. RM performed an updated literature search; verified the data extraction and statistical analyses; and rewrote the review in light of the suggestions of the reviewers. TP and CR approved the final version of the review.

DECLARATIONS OF INTEREST

The authors have no permanent financial contracts with companies producing interferon. T. Poynard, P. Opolon, and J.P. Zarski have been involved in prospective studies sponsored by Schering Plough, Roche, Glaxo Wellcome, and AMGEN.

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Internal sources

- No sources of support supplied

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- Club Francophone de l'Hypertension Portale, France.
- Recherche et Partage, France.

NOTES

Cochrane Database Syst Rev. 2002;(1):CD000369 'Interferon for acute hepatitis C'.

Erratum regarding listing of authors in MEDLINE. In stead of: Poynard T, Regimbeau C, Myers RP, Thevenot T, Leroy V, Mathurin P, Opolon P, Zarski JP

it should be: Myers RP, Regimbeau C, Thevenot T, Leroy V, Mathurin P, Opolon P, Zarski JP, Poynard T.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Antiviral Agents [*therapeutic use]; Hepatitis C [*drug therapy]; Interferon alpha-2; Interferon-alpha [*therapeutic use]; Interferon-beta [*therapeutic use]; Randomized Controlled Trials as Topic; Recombinant Proteins

MeSH check words

Humans