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Interferon for interferon naive patients with chronic hepatitis C (Review)

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[Intervention Review]

Interferon for interferon naive patients with chronic hepatitis C

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ABSTRACT

Background

A previous meta-analysis of interferon therapy in naive patients with chronic hepatitis C has documented its efficacy in achieving virologic clearance, and improving liver biochemistry and histology; however, since its publication additional trials have been reported.

Objectives

To evaluate the response to interferon in interferon naive patients with chronic hepatitis C. The effect of treatment dose and duration, and the response in patients with cirrhosis and those with normal aminotransferases was also investigated.

Search methods

The Cochrane Controlled Trials Register (Cochrane Library Issue 1, 1999), MEDLINE (January 1966 to December 1999), and reference lists were searched, and pharmaceutical companies were contacted for unpublished trials.

Selection criteria

Randomised clinical trials comparing interferon with placebo, no treatment, or different regimens of interferon were selected. Abstracts were excluded.

Data collection and analysis

The primary outcome measure was sustained disappearance of serum HCV RNA (virologic sustained response (SR)). Biochemical and end of treatment responses, liver histology, and adverse events were also recorded. Assessment of drug efficacy used the methods of Peto and Der Simonian and Laird.

Main results

Fifty-four trials enrolling 6545 patients were included. Compared with no treatment, interferon 3 MU thrice weekly for 12 months increased the probability of a virologic SR (Peto odds ratio (OR) 4.60; 95% confidence interval (CI) 1.53 to 13.85). At this dosage and duration of therapy, the rate of virologic SR was 17% (95% CI 10 to 28%) in interferon-treated patients versus 3% (95% CI 1 to 10%) in controls. A dose of 6 MU was more effective than 3 MU thrice weekly (OR for 12 months treatment, 2.21; 95% CI 1.10 to 4.45), as were durations of 12 months or greater versus six months (OR 1.87; 95% CI 1.30 to 2.67). Liver biochemistry responses were alike. Adverse events were more common with higher doses and prolonged durations of treatment. Compared with no therapy, interferon increased the probability of histologic improvement

(OR 9.22; 95% CI 5.69 to 14.94). The response to interferon in cirrhotic patients (virologic SR, 17%; 95% CI 11 to 26%) was similar to that in non-cirrhotic patients. However, interferon was no more effective than control in patients with normal aminotransferases.

Authors' conclusions

Interferon is effective in achieving viral clearance and improving liver biochemistry and histology in interferon naive patients with chronic hepatitis C. Higher doses and prolonged durations are more effective, but associated with more frequent adverse events. Interferon is associated with similar benefits in patients with cirrhosis, but the efficacy in patients with normal aminotransferases is unproven.

PLAIN LANGUAGE SUMMARY

Interferons show efficacy on virologic, biochemical, and histological outcomes in interferon naive patients with chronic hepatitis C

Hepatitis C virus infection can progress to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The goal of this systematic review was to examine the effects of interferon treatment for interferon naive (previously untreated) patients with chronic hepatitis C. This review confirmed the efficacy of interferon on surrogate outcomes as well as a favourable effect of higher treatment doses and prolonged durations. However, these effects were associated with more adverse events. Compared with non-cirrhotic patients, cirrhotic patients respond similarly, but the efficacy of interferon in patients with normal liver biochemistry is not substantiated by the data. Although interferon monotherapy is no longer considered the standard therapy for chronic hepatitis C, this review defines the optimal dose and duration of interferon monotherapy, which may be useful for patients who cannot tolerate combination therapy including interferon and ribavirin, the most effective therapy currently available.

BACKGROUND

Since the first meta-analysis of interferon therapy in chronic hepatitis C in which 18 randomised clinical trials (RCTs) were analysed (Tine 1991), at least 88 new references of interferon therapy and several other meta-analyses in the treatment of acute or chronic hepatitis C have been published. These studies have confirmed the efficacy of interferon in achieving viral clearance and improving liver biochemistry and histology. Several questions, however, remain to be answered including defining the optimal dosage and duration of interferon monotherapy, and determining the response in subgroups including those with cirrhosis and those with normal liver biochemistry. This systematic review serves to update these previous meta-analyses, and to address these unresolved issues.

OBJECTIVES

The a priori objectives of this review were to address the following questions:
1) What is the efficacy of interferon at a standard dose and duration (3 million international units (MU) injected thrice weekly (TIW) for six months) versus a control group (placebo or no intervention) in terms of alanine aminotransferase (ALT), normalisation, virologic response, and histological improvement?
2) Is an increase in the dose or duration of interferon treatment associated with an improved response in comparison to the standard regimen?
3) Is the response to interferon therapy different in the following subgroups: 1) patients with normal aminotransferases; and 2) patients with cirrhosis?

METHODS

Criteria for considering studies for this review

Types of studies

RCTs comparing interferon with placebo, no treatment, or different doses of interferon were included. Studies employing randomisation after an initial run-in period of interferon treatment were excluded as were those published as interim reports or abstracts only. There were no language limitations.

Types of participants

Chronic hepatitis C was defined as: 1) a positive serological test for HCV and detectable serum HCV ribonucleic acid (RNA) by polymerase chain reaction (PCR) assay; and 2) chronic hepatitis documented on liver biopsy. Only treatment-naive patients were included in the core analysis; trials involving previously treated patients (non-responders and relapsers) were excluded. Patients post liver transplantation or those coinfected with the hepatitis B virus and/or human immunodeficiency virus were also excluded.

Types of interventions

RCTs assessing interferon versus placebo, no treatment, or different regimens of interferon were included. There were no exclusions based on type, dose, or duration of interferon therapy.

Types of outcome measures

In order to be included, at least one of the following outcome measures had to be reported: normalisation of ALT activity at the end of treatment (biochemical ETR); sustained ALT normalisation at the end follow-up (biochemical SR); disappearance of serum HCV RNA by PCR at the end of the treatment (virologic ETR) and at the end of follow-up (virologic SR; the primary outcome measure). On examination of the included trials, we defined (post hoc) the time point following the end of treatment necessary for consideration of a sustained response as three months. The impact of interferon therapy on the rate of histologic improvement was assessed in patients with pre- and post-treatment liver biopsies. We did not plan an analysis of the effect of treatment on clinical outcomes because, in our previous experience, no such data was available. However, when such information was discovered on reviewing the RCTs, it was recorded.

Search methods for identification of studies

We searched The Cochrane Controlled Trials Register (Cochrane Library Issue 1, 1999) and MEDLINE (January 1966 to December 1999). All publications describing (or which might describe) RCTs of interferon treatment in patients with chronic hepatitis C 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 The Cochrane Controlled Trials Register and MEDLINE: 'hepatitis non-A non-B, -C' and 'clinical trial'. Furthermore, we searched the reference lists of the retrieved articles and published reviews, and contacted pharmaceutical companies to obtain unpublished RCTs.

Data collection and analysis

Meta-analyses were conducted according to a predetermined protocol following the recommendations of Sacks et al. (Sacks 1987). Methodological quality assessment 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 patients seen and excluded; number of subjects randomised in each group; number of participants 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): A) adequate (central randomisation, sealed envelopes, or similar); B) unclear (not described); C) inadequate (open table of random numbers or similar); and D) not used (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 when known, mode of infection, and type of interferon administered (alfa-2a, alfa-2b, lymphoblastoid, other).

Criteria of combinability
RCTs were combined only if at least one of the main outcome measures was assessed. For each RCT, the exact drug dosage was given as well as the duration of treatment. In the analysis of different interferon formulations, the following methods were used to assess combinability for each drug: 1) comparison of the

improvement in each outcome measure in the control groups with the Chi-square test; and 2) heterogeneity tests by the methods of Peto et al. (DeMets 1987) and Der Simonian and Laird (Der Simonian 1986).

Selection and data-extraction bias
All RCTs considered for inclusion were analysed independently by two observers (TP, TT, 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 (The Cochrane Collaboration) and NCSS 2001 (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. 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 fixed effects model (DeMets 1987). Where a random effects model was used, the word 'Random' appears after '95% confidence interval (CI)'. Comparisons between strata were performed using Peto odds ratios (OR); each estimate was reported with its 95% CI. A P-value of 0.05 or less was considered significant.

The following sensitivity analyses were performed after the inclusion or exclusion of appropriate RCTs from the core group of trials: 1) exclusion of RCTs with quality < median score; 2) exclusion of RCTs including patients with a prevalence of cirrhosis >30%; 3) exclusion of RCTs with a mean age > 47 years; 4) exclusion of RCTs with a mean disease duration > five years; 5) exclusion of RCTs with a follow-up of < 12 months (and therefore a definition of sustained response of < 12 months); and 6) exclusion of RCTs assessing non-alfa-2b interferons.

RESULTS

Description of studies

RCTs were described separately according to their control groups as either: 1) comparisons of interferon versus a control group receiving placebo or no treatment; or 2) comparisons of different regimens of interferon. The following clinical characteristics were described in the table 'Characteristics of included studies': first author, allocation concealment, blinding, intention-to-treat analysis, methodological score, interferon type, interferon schedule, follow-up, number of patients excluded, mean age, percentage of males, transfusion history, intravenous drug use, prevalence of cirrhosis, and mean disease duration.

A total of 54 RCTs including 6545 patients met the inclusion criteria for this meta-analysis, 21 trials more than the previous analysis (Poynard 1996). No unpublished RCTs were identified. Eight newly identified RCTs studied the effect of interferon therapy versus control, bringing the total number of eligible RCTs to 24 (Camps 1993; Capra 1993; Causse 1991; Cimino 1991; Davis 1989; Diodati 1994; Fernandez 1997; Furusyo 1997; Giudici 1991; Gomez-Rubio 1990; Ikeda 1998; Makris 1991; Marcellin 1991; Mazella 1994; Nishiguchi 1995; Reichen 1996; Rossini 1997; Rumi 1995; Saez-Royuela 1991; Saito 1994; Sangiovanni 1998; Saracco 1990; Valla 1999; Weiland 1990). Among the eight newly identified RCTs, one compared interferon administered for 12 months versus a tailored interferon and a separate untreated control arm (Reichen 1996), two RCTs were performed in patients with normal aminotransferases (Rossini 1997; Sangiovanni 1998), one in haemodialysis patients (Fernandez 1997), and four in cirrhotic patients only (Furusyo 1997; Ikeda 1998; Nishiguchi 1995; Valla 1999).

In comparison to our previous meta-analysis (Poynard 1996), 15 new RCTs comparing different doses or durations of interferon were identified bringing the total number of eligible RCTs to 24 (Alberti 1993; Chemello 1995; Craxi 1996; Degos 1998; Enriquez 1995; Garson 1997; Hagiwara 1993; Hakozaki 1995; Imai 1997; Jouet 1994; Kasahara 1995; Komatsu 1997; Laghi 1997; Lin 1995; Marcellin 1995; Matsumoto 1994; McHutchison 1998; Ouzan 1998; Poynard 1995; Saracco 1993; Shiratori 1997; Simon 1997; Tassopoulos 1996). There were 23 references for 24 RCTs because the Alberti et al. publication (Alberti 1993) included two RCTs. A total of 18 RCTs published in 17 full papers (Alberti 1993; Brouwer 1998; Chemello 1995; Enriquez 1995; Garson 1997; Hagiwara 1993; Hakozaki 1995; Imai 1997; Komatsu 1997; Laghi 1997; Lin 1995; Marcellin 1995; Matsumoto 1994; Ouzan 1998; Shiratori 1997; Simon 1997; Tassopoulos 1996) compared different doses of interferon, including nine comparisons of 'high' dose versus the 'standard' dose of 3 MU (for six months in six trials; for 12 months in four trials) (Alberti 1993; Chemello 1995; Garson 1997; Hagiwara 1993; Hakozaki 1995; Laghi 1997; Lin 1995; Simon 1997), and nine other comparisons (Brouwer 1998; Enriquez 1995; Imai 1997; Komatsu 1997; Ouzan 1998; Marcellin 1995; Matsumoto 1994; Tassopoulos 1996; Shiratori 1997). The randomisation process of one trial is suspect (Shiratori 1997); nevertheless, this trial has been included and the effect of its inclusion analysed via a sensitivity analysis. A total of ten RCTs assessing the effect of treatment duration were identified (Chemello 1995; Craxi 1996; Degos 1998; Garson 1997; Jouet 1994; Kasahara 1995; Lin 1995; McHutchison 1998, Poynard 1995, Saracco 1993).

A total of four RCTs were designed assessing therapy tailored to the response (biochemical or virologic) to treatment (Brouwer 1998; Fernandez 1997; Reichen 1996; Rumi 1996). Two of these trials, enrolling a total of 401 patients, included a control arm consisting of standard, fixed-dose interferon therapy in naive patients and were subjected to meta-analysis (Brouwer 1998; Reichen 1996). The remaining trials were excluded because they lacked a control arm treated with fixed-dose therapy (Fernandez 1997; Rumi 1996).

Four RCTs directly comparing different interferon preparations (beta interferon, consensus interferon, leukocyte interferon alfa, and lymphoblastoid interferon) with interferon alfa-2a or -2b in a total of 2330 patients were identified (Farrell 1998; Rumi 1996; Tong 1997; Villa 1996).

Risk of bias in included studies

The methodological quality of the included studies was graded according to a previously validated method which generates a score ranging from -2 to 28 (Poynard 1988). The median scored of the included studies was 13 (range, 8 to 21). The mean +/- standard deviation was 13.5 +/- 3.1. Allocation concealment was considered

adequate in only 14 of the included trials and outcomes were assessed by blinded reviewers in only six. Data were analysed according to the intention-to-treat method in 34 of the 54 trials.

Of the 54 RCTs included in the systematic review, only one (Villa 1996) reported both adequate allocation concealment and double blinding. Of the 24 RCTs comparing interferon with control, six had adequate allocation concealment (Camps 1993; Davis 1989; Furusyo 1997; Mazella 1994; Valla 1999; Weiland 1990) and two were double blinded (Causse 1991; Fernandez 1997). Of the 24 trials comparing different doses or durations of interferon, one (Garson 1997) was double blinded and five (Craxi 1996; Lin 1995; Marcellin 1995; McHutchison 1998; Poynard 1995) concealed allocation adequately. Of the four RCTs assessing therapy tailored to the response to treatment, one (Brouwer 1998) had adequate allocation concealment, and one (Fernandez 1997) was double-blinded. Of the four trials comparing different interferon preparations, the Villa et al. trial (Villa 1996), reported adequate allocation concealment and double blinding; two others (Rumi 1996; Tong 1997) were double blinded; and another (Farrell 1998) had adequate allocation concealment.

Effects of interventions

INTERFERON VERSUS PLACEBO/UNTREATED CONTROLS (Forrest plots 01.01 to 01.05)
Compared with control, interferon at a dosage of 3 MU thrice weekly for six months increased the probability of achieving a biochemical ETR (OR 10.30; 95% CI 6.42 to 16.52) and SR (OR 8.05; 95% CI 3.82 to 16.96). The rates of biochemical ETR and SR were 45% (95% CI 38 to 53%) and 23% (95% CI 16 to 31%), respectively in the interferon group, versus 2% (95% CI 1 to 6%) and 1% (95% CI 0 to 4%) in untreated controls. Virologic outcome was not reported in these trials.

Compared with control, interferon at a dosage of 3 MU thrice weekly for at least 12 months increased the probability of achieving a virologic ETR (OR 10.07; 95% CI 4.50 to 22.55) and SR (OR 4.60; 95% CI 1.53 to 13.85). The rates of virologic ETR and SR were 42% (95% CI 31 to 54%) and 17% (95% CI 10 to 28%), respectively in the interferon group, versus 2% (95% CI 0 to 8%) and 3% (95% CI 1 to 10%) in untreated controls. Interferon treatment was also associated with an increased probability of achieving a biochemical ETR (OR 11.07; 95% CI 6.84 to 17.91) and SR (OR 8.30; 95% CI 4.65 to 14.80). The rates of biochemical ETR and SR were 49% (95% CI 41 to 56%) and 32% (95% CI 25 to 39%), respectively in the interferon group, versus 2% (95% CI 1 to 6%) and 2% (95% CI 1 to 5%) in untreated controls.

There was no significant heterogeneity in these meta-analyses.

Liver histology (Forrest plot 01.05)
Information regarding the percentage of patients with histologic improvement was not supplied in any of the eight newly identified RCTs comparing interferon with control. Therefore, the previously reported results (Poynard 1996) remain valid. In summary, after six months of treatment (Causse 1991; Saracco 1990), interferon caused a non-significant increase in the rate of histologic improvement compared with control (OR 15.67; 95% CI Random 0.82 to 300.76). These results were heterogeneous (P = 0.057). The mean rate of improvement was 67% (33/49 patients) in the interferon 3 MU thrice weekly group versus 16% (7/45) in controls. After 12 months of treatment (Camps 1993; Makris 1991), the mean rate of histologic improvement was 91% (40/44) in the interferon group versus 30% (13/44) in the control group (OR 12.46; 95% CI 5.33 to 29.13). Six months following the end of treatment (Diodati 1994; Rumi 1995), the mean rate of histologic improvement was 55% (33/60) in the interferon group versus 17% (8/48) in controls (OR 7.74; 95% CI 3.31 to 18.08). Overall, regardless of the timing of the post-treatment liver biopsy, interferon was associated with histologic improvement in 69% (106/153) of treated patients versus only 20% (28/137) of controls (OR 9.22; 95% CI 5.69 to 14.94).

Patients with normal aminotransferases (Forrest plots 02.01 to 02.02)
Two RCTs including a total of 50 patients assessed the response to interferon in patients with normal aminotransferases (Rossini 1997; Sangiovanni 1998). Only virologic outcome measures were reported in these trials. Treatment with 3 MU of interferon thrice weekly (for six months in one trial; for 12 months in the other) was associated with a virologic ETR in 23% (95% CI 9 to 44%) versus 4% (95% CI 0 to 2%) of controls (OR 5.00; 95% CI 0.98 to 25.40; P = 0.05). This difference, however, did not persist during follow-up. Only 2/26 (8%; 95% CI 1 to 25%) of the interferon-treated patients versus 0/24 (0%; 95% CI 0 to 14%) of the controls achieved a virologic SR (OR 7.48; 95% CI 0.43 to 130.05). There was no significant heterogeneity in the data for patients with normal aminotransferases.

Patients with cirrhosis (Forrest plots 03.01 to 03.06)
Five RCTs included 330 patients with cirrhosis (Furusyo 1997; Ikeda 1998; Nishiguchi 1995; Saito 1994; Valla 1999). Two reported biochemical ETR (Saito 1994; Valla 1999) and three reported biochemical SR (Ikeda 1998; Saito 1994; Valla 1999). Compared with no treatment, interferon at a dosage of 3 MU thrice weekly (for six months in one trial; 12 months in the other) was associated with an increased probability of achieving a biochemical ETR (OR 9.75; 95% CI 2.65 to 35.90). A response was seen in 18% (10/57) of the interferon-treated patients versus none of the controls. Interferon was also associated with an increase in the probability of achieving a biochemical SR (OR 9.17; 95% CI 2.55 to 32.95). A biochemical SR was observed in 14% (11/71) of the interferon group versus only 1% (1/77) of the controls.

Three RCTs assessed virologic responses (Furusyo 1997; Ikeda 1998; Nishiguchi 1995). HCV RNA became undetectable significantly more often in patients receiving interferon than no treatment. The virologic ETR was 41% (41/100) in interferon-treated patients versus 0% (0/101) in controls (OR 12.16; 95% CI 6.15 to 24.05). Sustained responses were seen in 17% (17/100) of treated patients versus 0% (0/101) of controls (OR 8.84; 95% CI 3.29 to 23.77).

Three RCTs in a total of 218 cirrhotic patients supplied information regarding the occurrence of hepatocellular carcinoma (Ikeda 1998; Nishiguchi 1995; Valla 1999). In a post hoc intention-to-treat analysis, there was no difference in the incidence of hepatocellular carcinoma between interferon-treated patients (46/106, 43%) and controls (52/112, 46%) (OR 0.74; 95% CI 0.38 to 1.47). The Nisghiguchi et al. trial (Nishiguchi 1995), however, which contributed 90 of the total 218 patients, had a large loss to follow-up. After approximately seven years, 36/45 of the interferon-treated patients and 19/45 of the controls were unavailable for assessment. Their inclusion in the meta-analysis as treatment failures (i.e., cases of hepatocellular carcinoma using the intention-to-treat method) severely biased the results. In a sensitivity analysis excluding this trial (Forrest plot 03.06), there remained no significant difference in the incidence of hepatocellular carcinoma between interferon-

treated patients and controls (OR 0.50; 95% CI 0.21 to 1.21). In this revised post hoc analysis, the incidence of hepatocellular carcinoma in the interferon and control groups were 13% (8/61) and 24% (16/67), respectively (P = 0.17).

There was no significant heterogeneity in the meta-analyses of cirrhotic patients.

COMPARISON OF DIFFERENT INTERFERON REGIMENS

Dose effect: 6 MU versus 3 MU thrice weekly (Forrest plots 04.01 to 04.04)

For the comparison of 6 MU versus 3 MU for six months treatment duration, the biochemical ETR was 63% (95% CI 56 to 69%) in the 6 MU group versus 51% (95% CI 44 to 58%) in the 3 MU group (OR 1.64; 95% CI 1.10 to 2.44). The rates of biochemical SR were 27% (95% CI 22 to 34%) and 15% (95% CI 11 to 21%), respectively (OR 2.03; 95% CI 1.27 to 3.23). The higher dosage of interferon also increased the probability of achieving a virologic ETR (OR 2.23; 95% CI 1.13 to 4.41) and SR (OR 2.69; 95% CI 1.24 to 5.84). The virologic ETR was 51% (95% CI 39 to 63%) in the 6 MU group versus 32% (95% CI 22 to 45%) in the 3 MU group. The corresponding rates of virologic SR were 35% (95% CI 24 to 47%) and 16% (95% CI 8 to 27%), respectively. These data were homogeneous.

For the comparison of 6 MU versus 3 MU for at least 12 months treatment duration, the biochemical ETR was 69% (95% CI 60 to 76%) in the 6 MU group versus 57% (95% CI 49 to 64%) in the 3 MU group (OR 1.63; 95% CI 1.00 to 2.67). The rates of biochemical SR were 46% (95% CI 38 to 55%) and 29% (95% CI 22 to 36%), respectively (OR 2.08; 95% CI 1.30 to 3.34). The higher dosage of interferon also increased the probability of achieving a virologic ETR (OR 2.79; 95% CI 1.53 to 5.09) and SR (OR 2.21; 95% CI 1.10 to 4.45). The virologic ETR was 59% (95% CI 48 to 69%) in the 6 MU group versus 32% (95% CI 24 to 42%) in the 3 MU group. The corresponding rates of virologic SR were 43% (95% CI 32 to 55%) and 25% (95% CI 17 to 37%), respectively. These data were homogeneous.

For the analysis of a dose effect in trials examining other treatment regimens, there was a statistically significant treatment effect in favour of higher dose therapy for a biochemical SR (OR 1.50; 95% CI 1.10 to 2.05), and a nonsignificant increase in the rate of virologic SR (OR 1.39; 95% CI 0.98 to 1.97). A sensitivity analysis excluding the Shiratori et al. trial (Shiratori 1997), which had unclear randomisation, did not significantly impact these results.

Duration effect: interferon >= 12 months versus six months (Forrest plots 05.01 to 05.04)

In trials examining the impact of the duration of interferon treatment, there was no significant effect on the rates of biochemical or virologic response at the end of treatment. Sustained responses, however, were significantly more common in those receiving a prolonged duration of therapy. At a thrice weekly dosage of 3 MU, the rate of biochemical SR was 23% (95% CI 20 to 27%) in those treated for 12 months or more versus only 11% (95% CI 8 to 14%) in those receiving six months of treatment (OR 2.51; 95% CI 1.79 to 3.52). The corresponding rates of virologic SR were 14% (95% CI 11 to 19%) and 7% (95% CI 5 to 11%), respectively (OR 2.12; 95% CI 1.31 to 3.44).

The effect of treatment duration on sustained responses was also significant at the higher dose of 6 MU thrice weekly. Compared with a treatment duration of six months, therapy for 12 months or longer was associated with an increase in the rate of biochemical SR (OR 2.18; 95% CI 1.46 to 3.25) and a non-significant increase in the rate of virologic SR (OR 1.60; 95% CI 0.94 to 2.73). The rates of biochemical SR were 30% (95% CI 25 to 35%) in those receiving treatment for 12 months or longer versus only 17% (95% CI 13 to 22%) in those treated for six months. The corresponding rates of virologic SR were 22% (95% CI 17 to 29%) and 16% (95% CI 11 to 22%), respectively.

There was no significant heterogeneity in the meta-analyses assessing the effect of the duration of interferon therapy.

SENSITIVITY ANALYSES

Sensitivity analyses did not reveal any significant influence upon the results of the analyses assessing interferon versus control (excluding the normal aminotransferase and cirrhotic groups) nor interferon versus different interferon regimens (including the assessments of dose and duration effects) of the following factors: exclusion of RCTs with low methodological quality; a cirrhosis prevalence > 30%; mean age > 47 years; mean disease duration > five years; a follow-up of less than 12 months; or the exclusion of RCTs assessing non-2b interferons (data not shown). Due to the large number of trials with inadequate or unclear allocation concealment, a post hoc sensitivity analysis was performed to determine the impact of allocation concealment on the rates of biochemical ETR and SR (Forrest plots 08.01 to 08.02). The impact of allocation concealment on the primary outcome measure (the rate of virologic SR) was not examined because only one (Furusyo 1997) of the eight trials eligible for this analysis had adequate allocation concealment. In the post hoc sensitivity analysis, the adequacy of allocation concealment did not affect the likelihood of a biochemical ETR or SR (P < 0.05 for both comparisons).

COMPARISON OF DIFFERENT INTERFERON FORMULATIONS (Forrest plots 06.01 to 06.04)

There was significant heterogeneity in all of the outcome measures assessed in the comparison of different interferon formulations (P < 0.001 for all measures). Nevertheless, there appeared to be no significant differences in the rates of biochemical or virologic SR among the different formulations of interferon.

TRIALS WITH TAILORED REGIMENS (Forrest plots 07.01 to 07.04)

There were no statistically significant differences between tailored and fixed-dosed regimens for any of the outcome measures assessed, including the rate of virologic SR (OR 1.23; 95% CI 0.72 to 2.09).

ADVERSE EVENTS

Compared with those treated for six months, patients treated for longer durations with standard dose therapy (3 MU thrice weekly) were more likely to require treatment discontinuation (9% versus 5%, P < 0.001) or dosage reduction (15% versus 10%, P < 0.001). Likewise, these patients were more likely to experience a variety of adverse events, including flu-like syndromes (80% versus 64%, P < 0.001), depression (24% versus 12%, P < 0.001), and alopecia (20% versus 15%, P = 0.02). Patients receiving higher dose therapy (5-6 MU thrice weekly) were more likely to have leukopenia than those receiving standard dose therapy (10% versus 1%, P < 0.001).

DISCUSSION

This systematic review identified 54 published RCTs which met the inclusion criteria, compared with only 33 in a previous meta-analysis from our group (Poynard 1996). This increase in

information justified an updated review in order to examine the robustness of our previous results and to address several unresolved issues. Although interferon monotherapy has now been superseded by more effective therapy including pegylated interferon and ribavirin, this meta-analysis provides important information for those patients ineligible for, or who cannot tolerate ribavirin, and in places where pegylated interferon is not yet available. This review confirms the efficacy of interferon in achieving virologic clearance and thereby improving hepatic biochemistry and histology in naive patients with chronic hepatitis C. In fact, a standard course of interferon 3 MU thrice weekly for 12 months was associated with a virologic SR of 17% versus only 3% in controls. This led to a 30% absolute increase in the rate of sustained biochemical response and a tripling in the probability of histologic improvement during short-term follow-up.

It should be emphasised, however, that no clinical outcome measures were assessed in this meta-analysis, nor were they in any long-term, prospective studies. Therefore, in the absence of knowledge relating to the long-term potential of interferon to reduce important events, such as the incidence of endstage liver disease or requirement for liver transplantation, it is up to the patient and treating physician to decide whether or not to embark on interferon therapy based on surrogate evidence.

Our analysis confirmed a significant impact of dose on the response to interferon monotherapy. Treatment with 6 MU thrice weekly for 12 months was associated with a near doubling of the rate of virologic SR compared with the standard dose of 3 MU thrice weekly (43% versus 25%, P = 0.03). This rate of virologic SR is similar to that reported in recent, large-scale trials of combination therapy with ribavirin (McHutchison 1998; Poynard 1998). Admittedly, the relative success of interferon monotherapy in our review may relate in part to the insensitivity of PCR assays available during the period of the included trials. This significant 'dose-effect' persisted independent of treatment duration (for six months or 12 months and longer).

Our analysis also enabled us to determine the impact of treatment duration on the rate of biochemical and virologic response to interferon monotherapy. Treatment with 3 MU thrice weekly for 12 months or longer was associated with a doubling of the rate of virologic SR compared with a six-month course (14% versus 7%, P = 0.003). This effect appeared to be more important with lower dose therapy than high-dose therapy in which the increase in virologic SR according to treatment duration did not reach statistical significance (22% for 12 months or longer versus 16% for six months, P = 0.15). As previously observed, this 'duration effect' was not significant for virologic responses at the end of treatment demonstrating that the utility of long-term therapy is the prevention of relapse in patients who have successfully cleared the virus by 24 weeks.

We also analysed the responses to different interferon formulations (including consensus, beta, and lymphoblastoid interferon) and tailored regimens of therapy. Our results revealed no clear difference between the different interferon formulations. Likewise, we could not identify a more efficacious strategy than that employing a fixed dose and duration of therapy. We found no clear advantage in terms of biochemical or virologic sustained responses with escalating or de-escalating regimens according to the early response to therapy; although more effective than no treatment, these regimens were no more effective than standard, fixed-dose therapy.

Our systematic review also allowed us to address the utility of interferon in two important patient subgroups: those with normal aminotransferases, and cirrhotic patients, in whom interferon treatment had generated a considerable amount of controversy. In patients with normal liver biochemistry, interferon therapy was associated with a 19% increase in the rate of virologic ETR compared with controls (23% versus 4%), but this difference did not persist during follow-up as a virologic SR was seen in only 8% of treated patients versus 0% of controls (P = 0.17). This failure to identify a sustained difference, however, may reflect a type II (beta) error since only two trials in a total of 50 patients were assessed. A potential argument against the exclusion of these patients from treatment is the difficulty in defining a normal ALT if gender and body mass are not considered (Piton 1998). Furthermore, recent trials have failed to identify a threshold value for initial ALT which is predictive of a virologic SR to therapy (McHutchison 1998; Poynard 1998; Gordon 2000). Nevertheless, we cannot recommend interferon monotherapy in patients with normal aminotransferases based on the results of this meta-analysis. We would, however, recommend that these patients be enrolled in randomised, controlled trials assessing pegylated interferon and ribavirin to help clarify this issue.

The effectiveness of interferon was also assessed in trials enrolling patients with compensated cirrhosis. This meta-analysis confirms the utility of interferon therapy in this patient subgroup with respect to biochemical and virologic outcome measures. The percentage of cirrhotic patients with persistently normal ALT or undetectable serum HCV RNA after treatment (virologic SR of 17%) was significantly higher than in controls, and similar to that reported in non-cirrhotic patients. We could not, however, demonstrate a protective effect of interferon therapy on the progression to hepatocellular carcinoma in a post hoc analysis. Using a strict intention-to-treat analysis in a total of 218 patients, hepatocellular carcinoma developed in 43% of interferon-treated patients versus 46% of controls (P = 0.4) after a mean follow-up ranging from 3.3 to 5.5 years. Only well-designed, prospective trials with acceptable follow-up will clarify this issue in the future.

We also attempted to analyse the frequency of adverse events attributable to interferon, but this was difficult to interpret due to heterogeneity in the quality of reporting in the included trials. Our conclusions should also be tempered by the fact that all of the outcome measures were assessed in an unblinded fashion. Nevertheless, the six-month incidence of alopecia (15%) and depression (12%) represent meaningful information which can be supplied to patients prior to the initiation of therapy. Another clinically important point is the incidence of suicide related to interferon-induced depression. Unfortunately, we were unable to estimate this event due to insufficient data. From the available data it was also difficult to estimate the effects of dose and duration of interferon therapy on the incidence of adverse events. We did, however, observe a larger impact of treatment duration than dose, with the exception of leukopenia, which was significantly more common with high-dose therapy. Treatment duration had its most striking effect on the incidence of depression, which doubled from 12% in those treated for six months to 24% in patients treated for a year or longer. This result suggests that in clinical practice the risk of depression still exists in patients who have tolerated

the first six months of treatment. We did not assess the impact of interferon therapy on a number of common side effects including fatigue, influenza-like symptoms, and myalgias. However, in a recent systematic review of combination therapy with interferon and ribavirin versus interferon monotherapy (Kjaergard 2002) the incidence of these side effects in the monotherapy group was 55%, 61%, and 53%, respectively. In the same review, dosage reductions were necessary in 5% of patients and treatment was discontinued in 9%.

Our systematic review has several weaknesses. In this overview, we did not include RCTs identified only as abstracts; this may have caused a bias of publication. However, in our previous overview (Poynard 1996), the observed significant differences persisted in sensitivity analyses after the inclusion of RCTs published only as abstracts. Furthermore, the rates of virologic SR observed in our review are similar to those reported in the systematic review cited above (Kjaergard 2002). Thus, we feel that our assessment of the treatment effect of interferon is accurate. Another limitation of our systematic review is the suboptimal methodological quality of the included trials; only one of the 54 included RCTs had adequate allocation concealment and was double blinded. Nevertheless, sensitivity analyses stratifying trials according to methodological quality (defined according to a previously validated quality score) and allocation concealment revealed no significant effect on the results. Another weakness was our failure to combine individual patient data, which would have permitted a better analysis of the treatment effect by taking into account 'per-patient' heterogeneity in multivariate analyses. In comparison to our previous overview, there are now many trials which examined virologic characteristics. However, it was impossible to perform meta-analyses stratified by such factors as age, gender, genotype, viral load, and stage of fibrosis, which we now know are important factors in determining patients' response to interferon therapy as well as their long-term prognosis. When we did perform such an analysis in patients treated by interferon alone in two recent trials comparing interferon monotherapy with combination therapy including ribavirin (McHutchison 1998; Poynard 1998), we did find that these five factors (younger age, female sex, infection with non-genotype 1, low viral load, and absent or minimal fibrosis) were predictive of a sustained virologic response to interferon monotherapy (Poynard 2000).

An additional weakness of this meta-analysis was the absence of standardisation of the outcome measures among the included trials. For example, the definition of a biochemical response ranged from one to four consecutive, normal ALT determinations. Similarly, the sensitivity of PCR testing for virologic responses was not stated in some trials, and varied from 100 to more than 3000 copies/ml in others. Furthermore, the time following the end of treatment necessary for the definition of a sustained response varied markedly in the trials from four to 36 months. It is reassuring, however, that the majority of the trials defined a sustained virologic response, undoubtedly the most important outcome assessed, at six months or more following the end of treatment. We now know that negative HCV RNA PCR tests beyond this point are highly durable (Marcellin 1997). In addition, a sensitivity analysis excluding trials with less than 12 months of follow-up, and hence a definition of sustained response of less than 12 months, did not reveal a significant impact on the results. Finally, our histologic data is weakened by the absence of standardised histological outcome measures in most of the trials (Bedossa 1994) as well as the frequent absence of post-treatment biopsies, which are notoriously difficult to obtain. Even in trials which focus on histological criteria, the number of available follow-up biopsies is generally only between 50 and 60 per cent.

In comparison to our previously published meta-analysis (Poynard 1996), the total number of patients included in this analysis was considerably higher. However, the mean number of patients included per trial was still low, with only nine RCTs having more than 100 patients per intervention arm. This limitation was most evident in the comparison of different interferon regimens since this type of comparison requires more power than comparisons versus untreated controls. By updating the previous meta-analysis, however, we were able to increase the power of the present review, and thereby reduce the risk of false-negative conclusions due to small trials. We now have a better estimate of the exact level of efficacy of interferon monotherapy for the biochemical, virologic, and histologic outcome measures assessed, which may serve as a benchmark for future treatments in interferon naive patients with chronic hepatitis C.

AUTHORS' CONCLUSIONS

Implications for practice

Interferon is an effective therapy in naive patients with chronic hepatitis C (including those with cirrhosis) with respect to biochemical, virologic, and histological outcomes. There does not appear to be a significant impact of interferon formulation or the use of tailored regimens according to patient response on the sustained clearance of HCV RNA from serum. The efficacy of interferon monotherapy for achieving sustained virologic clearance is dependent on the dose and duration of therapy. The most effective regimen of interferon monotherapy for this outcome appears to be at least 6 MU thrice weekly for 12 months treatment duration but at a cost of more adverse events.

Implications for research

These results are useful as a better assessment of the benefits of novel treatments in chronic hepatitis C. In the future, results of ongoing trials of other antiviral regimens, including pegylated interferons and ribavirin, should be compared to these results.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alberti 1993

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 10.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 51/54 (RCT1); 61/58 (RCT2) Excluded: No data available (NDA). Mean age: 45/48 (RCT1); 44/47(RCT2) % males: 76/66 (RCT1); 69/63(RCT2) % transfusion: NDA % drug abuse: NDA % cirrhosis: 18/26 (RCT1); 13/19(RCT2) Genotypes: NDA Disease duration: NDA
Interventions	- RCT 1: Alfa-2a IFN 6 MU TIW x 6 mo vs 3 MU TIW x 6 mo - RCT 2: Alfa n-1 IFN 6 MU TIW x 6 mo; 3 MU TIW x 6 mo vs 3 MU TIW x 12 mo - Follow-up: 8 mo
Outcomes	- biochemical ETR and SR
Notes	

Risk of bias

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

Brouwer 1998

Methods	Allocation concealment: adequate (sealed envelopes). Blinding: no. Intention to treat: yes. Methodological score: 18.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 149/187 Excluded: NDA Mean age: 47/47 % males: 63/57 % transfusion: NDA % drug abuse: NDA % cirrhosis: 25/25 Genotypes: G1 (60/69%), G2 (11/8%), G3 (15/12%), other (13/10%) Disease duration: 14/12
Interventions	- Experimental 1: Alfa-2b IFN 3 MU TIW x 6 mo - Experimental 2: Alfa-2b IFN 6 MU TIW x 8 wk, then down-titration until ALT normalization and RNA -. IFN stopped if ALT did not normalize during the 6 MU TIW period or after 52 wk if ALT normalized but RNA +. - Follow-up: 6 mo

Brouwer 1998 *(Continued)*

Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Camps 1993

Methods	Allocation concealment: adequate (sealed envelopes). Blinding: no. Intention to treat: yes. Methodological score: 14.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 36/36 Excluded: 0/0 Mean age: 44/43 % males: 67/61 % transfusion: 31/50 % drug abuse: 17/8 % cirrhosis: 28/25 Genotypes: NDA Disease duration: 5 ???
Interventions	- Experimental: Alfa-n-1 IFN 3 MU/d x 8 weeks; 3 MU TIW x 3 mo; 1.5 MU TIW x 6mo - Control: no intervention - Follow-up: 15 mo
Outcomes	- biochemical ETR and SR - liver histology
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Capra 1993

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: no. Methodological score: 12.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C

Capra 1993 *(Continued)*

	Arms: 21/19 Excluded: 3/0 Mean age: 52/40 % males: 38/78 % transfusion: NDA % drug abuse: 19/42 % cirrhosis: 48/21 Genotypes: NDA Disease duration: NDA
Interventions	- Experimental: Alfa-2a IFN 6 MU TIW x 6 mo - Control: no intervention - Follow-up: 0
Outcomes	- biochemical ETR
Notes	

Risk of bias

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

Causse 1991

Methods	Allocation concealment: unclear. Blinding: yes. Intention to treat: yes. Methodological score: 13.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 30/30 Excluded: 2/1 Mean age: 47/50 % males: 43/37 % transfusion: 33/50 % drug abuse: 10/13 % cirrhosis: NDA Genotypes: NDA Disease duration: NDA
Interventions	- Experimental: Alfa-2b IFN 3 MU TIW x 6 mo - Control: placebo - Follow-up: 6 mo
Outcomes	- biochemical ETR and SR - liver histology
Notes	

Risk of bias

Causse 1991 *(Continued)*

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

Chemello 1995

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 16.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 59/61/54 Excluded: 4/4/2 Mean age: 42/47/44 % males: 75/62/74 % transfusion: NDA % drug abuse: NDA % cirrhosis: 15/20/19 Genotypes: G1(52/55/47), G2 (32/32/38), G3 (16/13/13), other (0/0/2) Disease duration: 5/6/6 ???
Interventions	- Experimental 1: Alfa-2a IFN 6 MU TIW x 6 mo; 3 MU TIW x 6 mo - Experimental 2: Alfa-2a IFN 3 MU TIW x 12 mo - Experimental 3: Alfa-2a IFN 6 MU TIW x 6 mo - Follow-up: 12 mo
Outcomes	- biochemical ETR and SR
Notes	

Risk of bias

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

Cimino 1991

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 12.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: n=33/33 Excluded: 0/0 Mean age: 51/48 % males: 36/46 % transfusion: NDA % drug abuse: NDA % cirrhosis: 61/48

Cimino 1991 *(Continued)*

	Genotypes: NDA Disease duration: NDA
Interventions	Experimental: Alfa-2a IFN 3 MU TIW x 6 mo Control : no intervention Follow-up: 4 mo
Outcomes	- biochemical ETR and SR
Notes	

Risk of bias

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

Craxi 1996

Methods	Allocation concealment: adequate (sealed envelopes). Blinding: no. Intention to treat: yes. Methodological score: 18.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 56/60 Excluded: 13/10 Mean age: 48/47 % males: 86/78 % transfusion: 100/100 % drug abuse: 0/0 % cirrhosis: 36/37 Genotypes: G1 (86/91), G2,3 (14/9) Disease duration: 4/5
Interventions	Experimental 1: Alfa-n-1 IFN 5 MU/m2 TIW x 2mo; 3 MU/m2 TIW x 10 mo Experimental 2: Alfa-n-1 IFN 5 MU/m2 TIW x 2mo; 3 MU/m2 TIW x 4 mo Follow-up: 12 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Davis 1989

Methods	Allocation concealment: adequate (allocation concealed centrally). Blinding: no Intention to treat: yes. Methodological score: 15.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 58/51 Excluded: 4/1 Mean age: 54/50 % males: 52/63 % transfusion: 90/82 % drug abuse: NDA % cirrhosis: 50/43 Genotypes: NDA Disease duration: NDA
Interventions	Experimental: Alfa-2b IFN 3 MU TIW x 6 mo Control: no intervention Follow-up: 6 mo
Outcomes	- biochemical ETR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Degos 1998

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 16.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 124/122 Excluded: 12/14 Mean age: 37/37 % males: 68/60 % transfusion: 33/28 % drug abuse: 31/32 % cirrhosis: 0/0 Genotypes: G1 (52/56), G2,3 (39/36), other (9/8) Disease duration: 11/12
Interventions	Experimental 1: Alfa-2a IFN 6 MU/d x 12d; 6 MU TIW x 22 wk; 3 MU TIW x 24 wk Experimental 2: Alfa-2a IFN 3 MU TIW x 24 wk Follow-up: 6 mo
Outcomes	- biochemical ETR and SR

Degos 1998 *(Continued)*

	- virologic SR
Notes	

Risk of bias

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

Diodati 1994

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 13.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 30/30 Excluded: 1/5 Mean age: 49/55 % males: 77/43 % transfusion: 23/23 % drug abuse: NDA % cirrhosis: 50/40 Genotypes: NDA Disease duration: 8/7
Interventions	Experimental: Alfa-2a IFN 6 MU TIW x 1mo; 3 MU x 3 mo; 1 MU TIW x 8 mo Control: no intervention Follow-up: 6 mo
Outcomes	- biochemical ETR and SR - liver histology
Notes	

Risk of bias

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

Enriquez 1995

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 13.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 45/45 Excluded: 2/0

Enriquez 1995 *(Continued)*

	Mean age: 49/47 % males: 64/67 % transfusion: 24/42 % drug abuse: NDA % cirrhosis: 9/11 Genotypes : NDA Disease duration: 5/4
Interventions	Experimental 1: Alfa-n-1 IFN 10 to 5 MU TIW x 6 mo Experimental 2: Alfa-n-1 IFN 5 to 3 MU TIW x 6 mo Follow-up: 9 mo
Outcomes	- biochemical ETR and SR
Notes	

Risk of bias

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

Farrell 1998

Methods	Allocation concealment: adequate (centralized computer). Blinding: no. Intention to treat: yes. Methodological score: 18.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 533/538 Excluded: 26/19 Mean age: 39/39 % males: 69/69 % transfusion: NDA % drug abuse: NDA % cirrhosis: 53/59 Genotypes: G1 (60/62%), G2,3 (34/34%), other (6/4%) Disease duration: NDA
Interventions	Experimental 1: Alfa-n-1 IFN 3 MU TIW x 6 mo Experimental 2 : Alfa-2b IFN 3 MU TIW x 6 mo Follow-up: 12 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Farrell 1998 *(Continued)*

Allocation concealment?	Low risk	A - Adequate

Fernandez 1997

Methods	Allocation concealment: unclear. Blinding: yes. Intention to treat: yes. Methodological score: 17.
Participants	NAIVE HEMODIALYSED PATIENTS WITH CHRONIC HEPATITIS C Arms: 14/9 Excluded: 3/2 Mean age: 44/49 % males: 36/67 % transfusion: 36/67 % drug abuse: 0/0 % cirrhosis: NDA Genotypes: G1 (54/78%), G2,3 (38/22%) Disease duration: 2/2
Interventions	Experimental: Alfa-2b IFN 1.5 MU TIW x 3 mo; increased to 3 MU TIW x 6 mo if ALT still elevated Control: placebo Follow-up: 18 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Risk of bias

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

Furusyo 1997

Methods	Allocation concealment: adequate (sealed envelopes). Blinding: no. Intention to treat: no. Methodological score: 14.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C AND CIRRHOSIS Arms: 41/41 Excluded: 7/0 Mean age: 59/58 % males: 49/58 % transfusion: 41/49 % drug abuse: 0/0 % cirrhosis: 100/100 Genotypes: G1 (78/73%), G2 (22/27%) Disease duration: NDA

Furusyo 1997 *(Continued)*

Interventions	Experimental: Alfa-n-1 IFN 6 MU/day x 2 wk; 6 MU TIW x 22 wk Control: no intervention Follow-up: 6 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Garson 1997

Methods	Allocation concealment: unclear. Blinding: yes. Intention to treat: yes. Methodological score: 15.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 12/10/8/8 Excluded: 0/0/0/0 Mean age: 39/39/38/41 % males: 75/80/62/50 % transfusion: NDA % drug abuse: 92/90/62/88 % cirrhosis: 25/10/0/0 Genotypes: G1 (67/50/38/38%), G2,3 (33/50/62/62) Disease duration: NDA
Interventions	Experimental 1: Alfa-n-1IFN 3 MU TIW x 6 mo Experimental 2: Alfa-n-1IFN 3 MU TIW x 12 mo Experimental 3: Alfa-n-1 IFN 5 MU TIW x 6 mo Experimental 4: Alfa-n-1 IFN 5 MU TIW x 12 mo Follow-up: 12 mo
Outcomes	- biochemical SR - virologic ETR and SR
Notes	

Risk of bias

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

Giudici 1991

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 12.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 15/15 Excluded: 0/0 Mean age: 50/33 % males: 60/80 % transfusion: 27/13 % drug abuse: 13/7 % cirrhosis: 13/13 Genotypes: NDA Disease duration: NDA
Interventions	Experimental: Alfa-2b IFN 3 MU TIW x 6 mo Control: no intervention Follow-up: 12 mo
Outcomes	- biochemical ETR and SR
Notes	

Risk of bias

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

Gomez-Rubio 1990

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 12.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 15/15 Excluded: 2/0 Mean age: 41/40 % males: 60/53 % transfusion: 60/73 % drug abuse: 7/7 % cirrhosis: 27/7 Genotypes: NDA Disease duration: 7/8
Interventions	Experimental: Alfa-2b IFN 5 MU TIW x 2 mo; 1.5 MU TIW x 16 mo Control: no intervention Follow-up: 6 mo

Gomez-Rubio 1990 *(Continued)*

Outcomes	- biochemical ETR and SR
Notes	

Risk of bias

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

Hagiwara 1993

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: no. Methodological score: 10.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 30/30 Excluded: 3/4 Mean age: 47/49 % males: 82/65 % transfusion: 22/42 % drug abuse: NDA % cirrhosis: NDA Genotypes: NDA Disease duration: NDA
Interventions	Experimental 1: Alfa-n-1 IFN 6 MU/day x 2 wk; 6 MU TIW x 6 mo Experimental 2: Alfa-n-1 IFN 3 MU/day x 2 wk; 3 MU TIW x 6 mo Follow-up: 6 mo
Outcomes	- biochemical ETR and SVR - virologic ETR and SR
Notes	

Risk of bias

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

Hakozaki 1995

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: no. Methodological score: 11.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 26/35

Hakozaki 1995 *(Continued)*

	Excluded: 0/1 Mean age: 46/46 % males: 92/94 % transfusion: 46/43 % drug abuse: NDA % cirrhosis: 31/29 Genotypes: G1 (73/71%), G2 (23/26%), G3 (4/3%) Disease duration: NDA
Interventions	Experimental 1: 6 MU TIW x 6 mo Experimental 2: 3 MU TIW x 6 mo Follow-up: 12 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Risk of bias

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

Ikeda 1998

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: no. Methodological score: 10.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C AND CIRRHOSIS Arms: 14/15 Excluded: 1/0 Mean age : 52/57 % males: NDA % transfusion: NDA % drug abuse: NDA % cirrhosis: 100/100 Genotypes : G2 (100/100%) Disease duration: NDA
Interventions	Experimental: Alfa-2a IFN 9 MU TIW x 6 mo Control: no intervention Follow-up: 3 mo
Outcomes	- biochemical SR - virologic ETR and SR - incidence of hepatocellular carcinoma
Notes	

Risk of bias

Ikeda 1998 *(Continued)*

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

Imai 1997

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 11.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 44/44 Excluded: 2/2 Mean age: 53/53 % males: 66/75 % transfusion: 18/20 % drug abuse: NDA % cirrhosis: 0/0 Genotypes: G1 (83/79%), G2 (14/18%), other (3/3%) Disease duration: NDA
Interventions	Experimental 1: Alfa-2a IFN 6 MU/day x 2wk; 6 MU TIW x 22 wk Experimental 2: Alfa-2a IFN 6 MU/d x 2 wk; 3 MU TIW x 22 wk Follow-up: 6 mo
Outcomes	- biochemical ETR and SR - virologic SR
Notes	

Risk of bias

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

Jouet 1994

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 13.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 56/52 Excluded: >5 Mean age: 47/50 % males: 100/100 % transfusion: 57/79 % drug abuse: 29/19 % cirrhosis: 19/16

Jouet 1994 *(Continued)*

	Genotypes: NDA Disease duration: NDA
Interventions	Experimental 1: Alfa-2b IFN 3 MU TIW x 6 mo; 2 MU TIW x 3mo; 1 MU TIW x 3 mo Experimental 2: Alfa-2b IFN 3 MU TIW x 6 mo Follow-up: 6 mo
Outcomes	- biochemical ETR and SR
Notes	

Risk of bias

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

Kasahara 1995

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 12.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 45/48 Excluded: 2/3 Mean age: 47/47 % males: 86/78 % transfusion: 31/23 % drug abuse: NDA % cirrhosis: 0 Genotypes: G1 (65/82%), G2 (28/13%), other (7/4%) Disease duration: 9/8
Interventions	Experimental 1: Alfa-n-1 IFN 5 MU TIW x 6 mo; 5 MU twice weekly x 6 mo Experimental 2: Alfa-n-1 IFN 5 MU TIW x 6 mo Follow-up: 6 mo
Outcomes	- biochemical ETR and SR
Notes	

Risk of bias

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

Komatsu 1997

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: no. Methodological score: 8.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 26/25 Excluded: 2/5 Mean age : 50/50 % males: 50/72 % transfusion: NDA % drug abuse: NDA % cirrhosis: NDA Genotypes: G1(92/80%) Disease duration: NDA
Interventions	Experimental 1: Alfa-n-3 IFN 6 MU/day 6 days/wk x 8 wk; 6 MU TIW x 16 wk Experimental 2: Alfa-n-3 IFN 6 MU/day 6 days/wk x 2 wk; 6 MU TIW x 22 wk Follow-up: 6 mo
Outcomes	- virologic ETR and SR
Notes	

Risk of bias

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

Laghi 1997

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: no. Methodological score: 8.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 14/31 Excluded: 3/0 Mean age : NDA % males: NDA % transfusion: NDA % drug abuse: NDA % cirrhosis: 0/6 Genotypes: NDA Disease duration: NDA
Interventions	Experimental 1: Alfa-n-3 IFN 6 MU TIW x 12 mo Experimental 2 : Alfa-n-3 IFN 3 MU TIW x 12 mo Follow-up: 12 mo
Outcomes	- biochemical ETR and SR

Laghi 1997 *(Continued)*

Notes	

Risk of bias

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

Lin 1995

Methods	Allocation concealment: adequate (sealed envelopes). Blinding: no. Intention to treat: yes. Methodological score: 16.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 75/72/83 Excluded: 7/7/18 Mean age: 39/38/42 % males: 76/72/63 % transfusion: 21/19/24 % drug abuse: 47/46/37 % cirrhosis: 41/31/30 Genotypes: NDA Disease duration: NDA
Interventions	Experimental 1: Alfa-2b IFN 5 MU TIW x 6 mo Experimental 2: 3 MU TIW x 6 mo Experimental 3: 3 MU TIW x 24 mo Follow-up: 24 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Makris 1991

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 12.
Participants	NAIVE HEMOPHILIACS WITH CHRONIC HEPATITIS C Arms: 10/8 Excluded: 1/0

Makris 1991 *(Continued)*

	Mean age: 38/38 % males: 100/100 % transfusion: 100/100 % drug abuse: 0/0 % cirrhosis: 10/12 Genotypes: NDA Disease duration: NDA
Interventions	Experimental: Alfa-2b IFN 1 MU TIW x 1 mo; 2 MU TIW x 1 mo; 3 MU TIW x 10 mo Control: no intervention Follow-up: 15 mo
Outcomes	- biochemical ETR - liver histology
Notes	

Risk of bias

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

Marcellin 1991

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: no. Methodological score: 12.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 18/18 Excluded: 2/0 Mean age: 42/41 % males: 67/50 % transfusion: 50/56 % drug abuse: 28/28 % cirrhosis: 17/11 Genotypes: NDA Disease duration: 4/4
Interventions	Experimental: Alfa-2b IFN 3 MU TIW x 6 mo Control: no intervention Follow-up: 6 mo
Outcomes	- biochemical ETR and SR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Marcellin 1991 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Marcellin 1995

Methods	Allocation concealment: adequate (sealed envelopes). Blinding: no. Intention to treat: no. Methodological score: 15.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 50/25 Excluded: 7/1 Mean age: 43/44 % males: 53/68 % transfusion: 62/68 % drug abuse: 32/32 % cirrhosis: 8/20 Genotypes: NDA Disease duration: 12/12
Interventions	Experimental 1: AlFa-2b IFN 3 MU TIW x 8 wk; 5 MU TIW x 8 wk; 10 MU TIW x 8 wk Experimental 2: Alfa-2b IFN 3 MU TIW x 6 mo Follow-up: 6 mo
Outcomes	- biochemical ETR and SR
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Matsumoto 1994

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 8.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 12/12 Excluded: 0/0 Mean age: 48/45 % males: 75/74 % transfusion: 25/33 % drug abuse: NDA % cirrhosis: NDA Genotypes: G1 (75/75%), G2(25/25%) Disease duration: NDA

Matsumoto 1994 *(Continued)*

Interventions	Experimental 1: Alfa-2a IFN 9 MU/day x 2 wk; 9 MU TIW x 6 mo Experimental 2: Alfa-2a IFN 3 MU/day x 2 wk; 3 MU x 6 mo Follow-up: 6 mo
Outcomes	- biochemical SR
Notes	

Risk of bias

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

Mazella 1994

Methods	Allocation concealment: adequate (sealed envelopes). Blinding: no. Intention to treat: no. Methodological score: 13.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 30/30 Excluded: 1/0 Mean age: 45/48 % males: 68/50 % transfusion: NDA % drug abuse: NDA % cirrhosis: NDA Genotypes: NDA Disease duration: 5/5
Interventions	Experimental: Alfa-n-1 IFN 3 MU TIW x 12 mo Control: no intervention Follow-up: 16 mo
Outcomes	- biochemical ETR and SR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

McHutchison 1998

Methods	Allocation concealment: adequate (centralized computer). Blinding: no.

McHutchison 1998 *(Continued)*

	Intention to treat: no. Methodological score: 20.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 231/225 Excluded: NDA Mean age: 45/44 % males: 75/75 % transfusion: 8/10 % drug abuse: 23/23 % cirrhosis: 3/2 Genotypes: G1(78/72%), G2,3 (21/28%), other (1/0%) Disease duration: 19/19
Interventions	Experimental 1: Alfa-2b IFN 3MU TIW x 12 mo Experimental 2: Alfa-2b IFN 3MU TIW x 6 mo Follow-up: 6 mo
Outcomes	- biochemical SR - virologic ETR and SR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Nishiguchi 1995

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: no. Methodological score: 18.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C AND CIRRHOSIS Arms: 45/45 Excluded: 0/0 Mean age: 55/57 % males: 62/51 % transfusion: NDA % drug abuse: NDA % cirrhosis: 100/100 Genotypes: G1 (73/80%), G2 (27/20%) Disease duration: 25/26
Interventions	Experimental: Alfa-n-1 IFN 6MU TIW x 12-24 wk. Six patients received a second course of treatment. Control: no intervention Follow-up: 24 mo
Outcomes	- virologic ETR and SR - incidence of hepatocellular carcinoma

Nishiguchi 1995 *(Continued)*

Notes	

Risk of bias

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

Ouzan 1998

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 15.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 149/142 Excluded: 10/14 Mean age: 48/48 % males: 89/92 % transfusion: 42/39 % drug abuse: NDA % cirrhosis: 20/23 Genotypes : NDA Disease duration: 4/4
Interventions	Experimental 1: Alfa-2a IFN 6MU TIW x 3mo; 3MU TIW x 3 mo Experimental 2: Alfa-2a IFN 3MU TIW x 6 mo Follow-up: 6 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Risk of bias

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

Poynard 1995

Methods	Allocation concealment: adequate (sealed envelopes). Blinding: no. Intention to treat: yes. Methodological score: 16.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 103/99/101 Excluded: 31/0/0 Mean age: 49/50/51

Poynard 1995 *(Continued)*

	% males: 51/49/55 % transfusion: 52/47/45 % drug abuse: NDA % cirrhosis: 27/23/27 Genotypes : NDA Disease duration: 6/7/9
Interventions	Experimental 1: Alfa-2b IFN 3MU TIW x 18 mo Experimental 2: Alfa-2b IFN 3MU TIW x 6 mo Experimental 3: Alfa-2b IFN 3MU TIW x 6mo; 1MU TIW x 12 mo Follow-up: 24 mo
Outcomes	- biochemical ETR and SR - virologic SR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Reichen 1996

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: no. Methodological score: 13.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 34/31/30 Excluded: 5/6/6 Mean age: 45/51/47 % males: 68/71/73 % transfusion: 35/26/20 % drug abuse: NDA % cirrhosis: 26/35/27 Genotypes: NDA Disease duration: NDA
Interventions	Experimental 1: Alfa-2b IFN 5MU TIW x 1 mo; decreased by 1MU each wk as long as ALT remained normal; if ALT did not normalize, a higher dose was reintroduced Experimental 2: Alfa-2b IFN 3MU TIW x 12 mo Control: no intervention Follow-up: 12 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Reichen 1996 *(Continued)*

Risk of bias

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

Rossini 1997

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 10.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C AND NORMAL ALT Arms: 10/9 Excluded: 0/0 Mean age: 51/51 % males: 60/50 % transfusion: NDA % drug abuse: 0/0 % cirrhosis: 0/0 Genotypes: G1 (20/56%), G2 (80/44%) Disease duration: NDA
Interventions	Experimental: Alfa-2b IFN 3MU TIW x 12 mo; stopped if RNA + at 6 mo Control: no intervention Follow-up: 12 mo
Outcomes	- virologic ETR and SR
Notes	

Risk of bias

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

Rumi 1995

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: no. Methodological score: 16.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 38/36 Excluded: 3/4 Mean age: 48 % males: 63 % transfusion: NDA % drug abuse: NDA

Rumi 1995 *(Continued)*

	% cirrhosis: 31 Genotypes: NDA Disease duration: NDA
Interventions	Experimental: Alfa-2a IFN 6MU TIW x 2 mo; 3MU TIW x 10 mo Control: no intervention Follow-up: 12 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR - liver histology
Notes	

Risk of bias

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

Rumi 1996

Methods	Allocation concealment: unclear. Blinding: yes. Intention to treat: no. Methodological score: 16.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 116/118 Excluded: 13/11 Mean age : 49/48 % males: 69/67 % transfusion: 16/19 % drug abuse: 7/8 % cirrhosis: 26/31 Genotypes: G1 (63/53%), G2,3 (33/43%), other (4/3%) Disease duration: NDA
Interventions	Experimental 1: Alfa-n-1 IFN 6MU TIW until ALT normal then 3 MU TIW x total of 12 mo Experimental 2: Alfa-2a IFN 6MaU TIW until ALT normal at least 4 wk then 3 MU TIW x total of 12 mo In both groups, if ALT broke through, the 6MU dose was reintroduced; IFN was stopped if ALT not normal within 24 wk. Follow-up: 12 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Rumi 1996 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Saez-Royuela 1991

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 12.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 10/10 Excluded: 2/0 Mean age : 36/39 % males: 60/60 % transfusion: 40/50 % drug abuse: NDA % cirrhosis: 30/30 Genotypes: NDA Disease duration: 4/7
Interventions	Experimental: Alfa-2c IFN 15 MU TIW x 3 mo; 10 MU TIW x 3 mo; 5 MU TIW x 6 mo Control: no intervention Follow-up: 6 mo
Outcomes	- virologic ETR and SVR
Notes	

Risk of bias

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

Saito 1994

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score:10.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 10/10 Excluded: 0/0 Mean age: 59/63 % males: 20/50 % transfusion: 40/50 % drug abuse: NDA % cirrhosis: 100/100 Genotypes: NDA Disease duration: NDA

Saito 1994 *(Continued)*

Interventions	Experimental: Alfa-n-1 IFN 3 MU TIW x 6 mo Control: no intervention Follow-up: 6 mo
Outcomes	- biochemical ETR and SVR
Notes	

Risk of bias

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

Sangiovanni 1998

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 16.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C AND NORMAL ALT Arms: 16/15 Excluded: 0/0 Mean age: 43/46 % males: 50/47 % transfusion: 31/33 % drug abuse: NDA % cirrhosis: 0/0 Genotypes: G1 (38/47%), G2 (50/47%), other (12/6%) Disease duration: NDA
Interventions	Experimental: Alfa-2a IFN 3 MU TIW x 6 mo Control: no intervention Follow-up: 6 mo
Outcomes	- virologic ETR and SR
Notes	

Risk of bias

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

Saracco 1990

Methods	Allocation concealment: unclear. Blinding: no.

Saracco 1990 *(Continued)*

	Intention to treat: no. Methodological score: 12.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 26/25 Excluded: 3/5 Mean age: 48/47 % males: 62/60 % transfusion: 46/48 % drug abuse: 54/52 % cirrhosis: 50/24 Genotypes: NDA Disease duration: NDA
Interventions	Experimental: IFN 3 MU TIW x 6 mo Control: no intervention Follow-up: 6 mo
Outcomes	- biochemical ETR and SR - liver histology
Notes	

Risk of bias

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

Saracco 1993

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 10.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 14/26 Excluded: NDA Mean age: NDA % males: NDA % transfusion: NDA % drug abuse: NDA % cirrhosis: NDA Genotypes: NDA Disease duration: NDA
Interventions	Experimental 1: Alfa-2b IFN 3 MU TIW x 12 mo Experimental 2: Alfa-2b IFN 3 MU TIW x 6 mo Follow-up: 36 mo
Outcomes	- biochemical ETR and SR

Saracco 1993 *(Continued)*

Notes	

Risk of bias

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

Shiratori 1997

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 17.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 133/139 Excluded: 0/0 Mean age: 47/53 % males: 73/62 % transfusion: 46/51 % drug abuse: NDA % cirrhosis: 0/0 Genotypes: G1 (81/74%), G2 (19/26%) Disease duration: NDA
Interventions	Experimental 1: Alfa-nat IFN 9 MU TIW x 6 mo Experimental 2: Alfa-nat IFN 6 MU TIW x 6 mo Follow-up: 12 mo
Outcomes	- virologic ETR and SR
Notes	

Risk of bias

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

Simon 1997

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: yes. Methodological score: 10
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 18/19/17/23 Excluded: 0/5/1/5 Mean age: 47/45/44/43 % males: 83/74/71/78

Simon 1997 *(Continued)*

	% transfusion: 39/16/35/26 % drug abuse: 50/53/65/52 % cirrhosis: 28/31/24/17 Genotypes: G1 (50/47/82/52%), G2 (39/11/6/17%), other (11/42/12/31%) Disease duration: NDA
Interventions	Experimental 1: Alfa-n-3 IFN 1 MU TIW x 6 mo Experimental 2: Alfa-n-3 IFN 2.5 MU TIW x 6 mo Experimental 3: Alfa-n-3 IFN 5 MU TIW x 6 mo Experimental 4: Alfa-n-3 IFN 10 MU TIW x 6 mo Follow-up: 6 mo
Outcomes	- biochemical ETR and SR
Notes	

Risk of bias

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

Tassopoulos 1996

Methods	Allocation concealment: unclear. Blinding: no. Intention to treat: no. Methodological score: 10.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 28/30 Excluded: 2/2 Mean age: 42/42 % males: 71/70 % transfusion: 11/20 % drug abuse: 29/20 % cirrhosis: 32/30 Genotypes: G1 (46/31%), G2,3 (32/55%), other (21/14%) Disease duration: NDA
Interventions	Experimental 1: Alfa-2a IFN 10 MU TIW x 6 mo Experimental 2: Alfa-2a IFN 3 MU TIW x 6 mo Follow-up: 6 mo
Outcomes	- biochemical ETR and SR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Tassopoulos 1996 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Tong 1997 (CIFN 3µg)

Methods	Allocation concealment: unclear. Blinding: yes. Intention to treat: yes. Methodological score: 21.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 232/240 Excluded: NDA Mean age: 43/43 % males: 72/72 % transfusion: 27/22 % drug abuse: 40/44 % cirrhosis: 39/24 Genotypes: NDA Disease duration: NDA
Interventions	Experimental 1: C-IFN 3 µg TIW x 6 mo Experimental 2: Alfa-2b IFN 15 µg TIW x 6 mo Follow-up: 6 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Risk of bias

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

Tong 1997 (CIFN 9µg)

Methods	Allocation concealment: unclear. Blinding: yes. Intention to treat: yes. Methodological score: 21.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 232/240 Excluded: NDA Mean age: 43/43 % males: 72/72 % transfusion: 22/22 % drug abuse: 46/44 % cirrhosis: 35/24 Genotypes: NDA Disease duration: NDA

Tong 1997 (CIFN 9µg) *(Continued)*

Interventions	Experimental 1: C-IFN 9 µg TIW x 6 mo Experimental 2: Alfa-2b IFN 15 µg TIW x 6 mo Follow-up: 6 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Risk of bias

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

Valla 1999

Methods	Allocation concealment: adequate (centralized randomisation; table of random numbers). Blinding: no. Intention to treat: yes. Methodological score: 16.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 47/52 Excluded: 10/13 Mean age: 57/56 % males: 70/61 % transfusion: 36/36 % drug abuse: 4/6 % cirrhosis: 100/100 Genotypes: G1 (50/63%), G2,3 (42/29), other (8/8%) Disease duration: 9/11
Interventions	Experimental: Alfa-2b IFN 3 MU TIW x 6 mo Control: no intervention. Ten patients received IFN treatment after follow-up wk 72. Follow-up: 12 mo
Outcomes	- biochemical ETR and SR - incidence of hepatocellular carcinoma
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Villa 1996 (bet-IFN)

Methods	Allocation concealment: adequate (centralized computer). Blinding: yes. Intention to treat: yes. Methodological score: 16.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 20/19/21 Excluded: 1/1/1 Mean age: 46/41/45 % males: 70/79/71 % transfusion: 5/11/10 % drug abuse: 10/10/5 % cirrhosis: 7/7/3 Genotypes: NDA Disease duration: NDA
Interventions	Experimental 1: Alfa-n3 IFN 3 MU TIW x 6 mo Experimental 2: Beta-IFN 3 MU TIW x 6 mo Experimental 3: Alfa-2b IFN 3 MU TIW x 6 mo Follow-up: 30 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Villa 1996 (leu-IFN)

Methods	Allocation concealment: adequate (centralized computer). Blinding: yes. Intention to treat: yes. Methodological score: 16.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 20/19/21 Excluded: 1/1/1 Mean age: 46/41/45 % males: 70/79/71 % transfusion: 5/11/10 % drug abuse: 10/10/5 % cirrhosis: 7/7/3 Genotypes: NDA Disease duration: NDA
Interventions	Experimental 1: Alfa-n3 IFN 3 MU TIW x 6 mo Experimental 2: Beta-IFN 3 MU TIW x 6 mo

Villa 1996 (leu-IFN) *(Continued)*

	Experimental 3: Alfa-2b IFN 3 MU TIW x 6 mo Follow-up: 30 mo
Outcomes	- biochemical ETR and SR - virologic ETR and SR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Weiland 1990

Methods	Allocation concealment: adequate (sealed envelopes). Blinding: no. Intention to treat: no. Methodological score: 13.
Participants	NAIVE PATIENTS WITH CHRONIC HEPATITIS C Arms: 21/12 Excluded: 2/0 Mean age: 54/56 % males: 91/92 % transfusion: 100/100 % drug abuse: 0/0 % cirrhosis: 0/0 Genotypes: NDA Disease duration: 3/4
Interventions	Experimental: Alfa-2b IFN 3 MU TIW x 9 mo Control: no intervention Follow-up: 12 mo
Outcomes	- biochemical ETR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

ALT: alanine aminotransferase
NDA: no data available.
TIW: thrice each week.
wk: weeks.
mo: months.
naive patients: naive to previous interferon treatment.
vs: versus.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Angelini 1995	Quasi-randomised trial.
Bonkovsky 1996	Trial in non-responders and relapsers.
Bresci 1996	Trial in non-responders.
Caporaso 1993	Quasi-randomised trial.
Chemello 1997	Trial in non-responders and relapsers.
Di Marco 1997	Randomised patients after initial course of therapy.
Ferenci 1996	Trial in non-responders.
Friedlander 1996	Quasi-randomised trial.
Heathcote 1998	Trial in non-responders and relapsers.
Lindsay 1996	Randomised patients after initial course of therapy.
Payen 1998	Trial in relapsers.
Poynard 1999	Trial in relapsers.
Rolachon 1997	Trial in non-responders.
Saracco 1997	Randomised patients after initial course of therapy.
Sheiner 1998	Liver transplant recipients.
Shiffman 1996	Randomised patients after initial course of therapy.

DATA AND ANALYSES

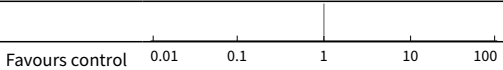
Comparison 1. Interferon vs. control

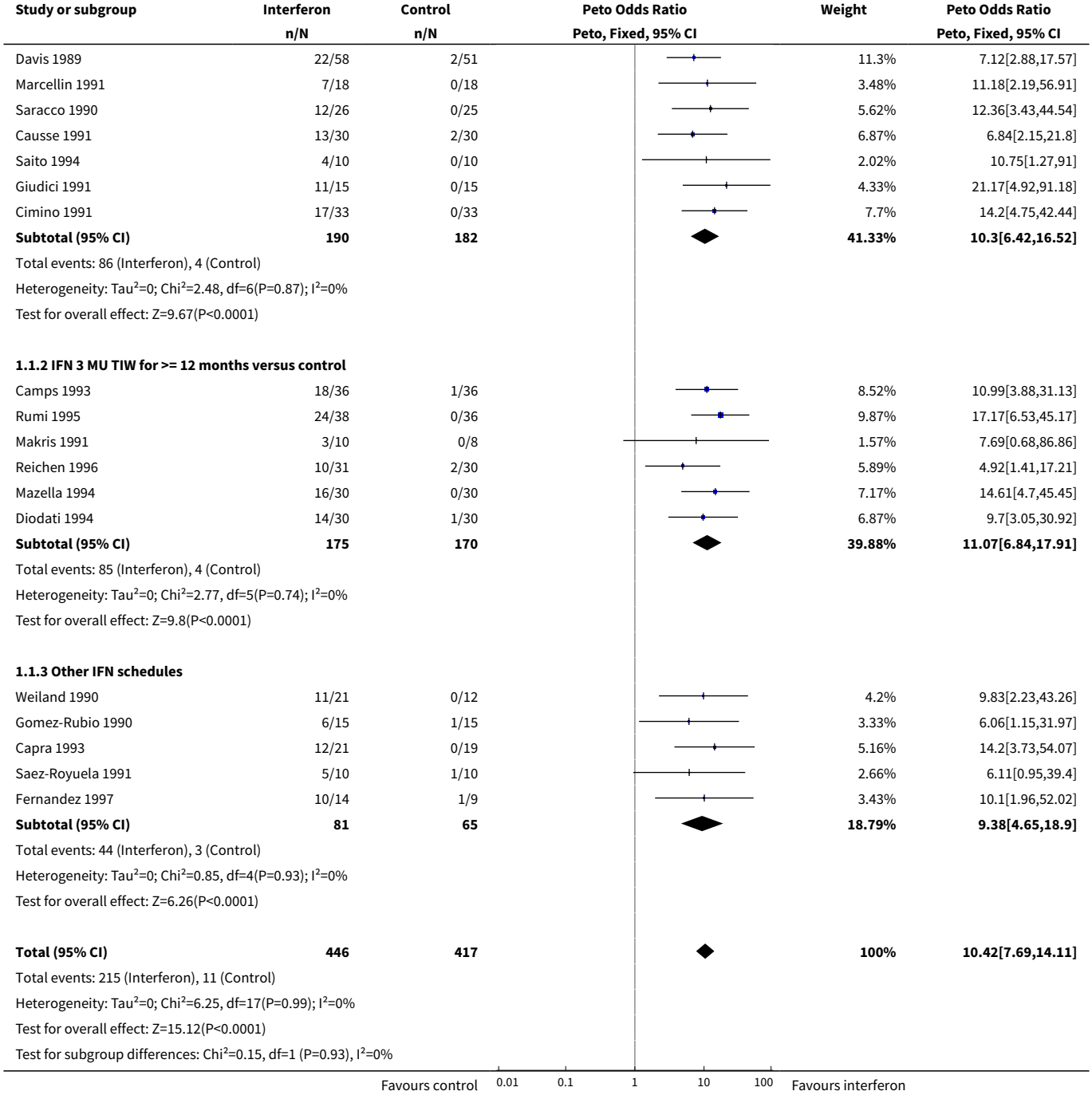
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Biochemical ETR	18	863	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.42 [7.69, 14.11]
1.1 IFN 3 MU TIW for 6 months versus control	7	372	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.30 [6.42, 16.52]
1.2 IFN 3 MU TIW for >= 12 months versus control	6	345	Peto Odds Ratio (Peto, Fixed, 95% CI)	11.07 [6.84, 17.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Other IFN schedules	5	146	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.38 [4.65, 18.90]
2 Biochemical SR	15	692	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.32 [5.50, 12.59]
2.1 IFN 3 MU TIW for 6 months versus control	6	263	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.05 [3.82, 16.96]
2.2 IFN 3MU TIW for >= 12 months versus control	5	327	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.30 [4.65, 14.80]
2.3 Other IFN schedules	4	102	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.87 [3.33, 23.64]
3 Virologic ETR	8	409	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.20 [6.29, 16.53]
3.1 IFN 3MU TIW for >= 12 months versus control	2	135	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.07 [4.50, 22.55]
3.2 Other IFN schedules	6	274	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.27 [5.61, 18.78]
4 Virologic SR	8	409	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.59 [3.30, 13.17]
4.1 IFN 3 MU TIW for >= 12 months versus control	2	135	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.60 [1.53, 13.84]
4.2 Other IFN schedules	6	274	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.34 [3.43, 20.28]
5 Improvement in liver histology	6	290	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.22 [5.69, 14.94]
5.1 Biopsy at the end of treatment (6 months)	2	94	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.21 [3.64, 18.53]
5.2 Biopsy at the end of treatment (12 months)	2	88	Peto Odds Ratio (Peto, Fixed, 95% CI)	12.46 [5.33, 29.13]
5.3 Biopsy at the end of follow-up (6 months following the end of treatment)	2	108	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.74 [3.31, 18.08]

Analysis 1.1. Comparison 1 Interferon vs. control, Outcome 1 Biochemical ETR.

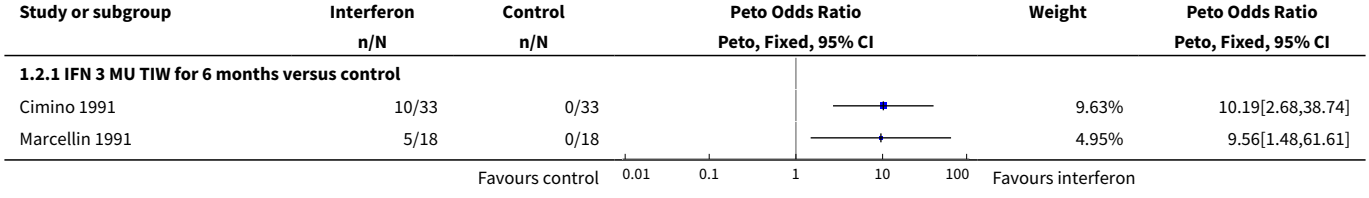
Study or subgroup	Interferon n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 IFN 3 MU TIW for 6 months versus control					



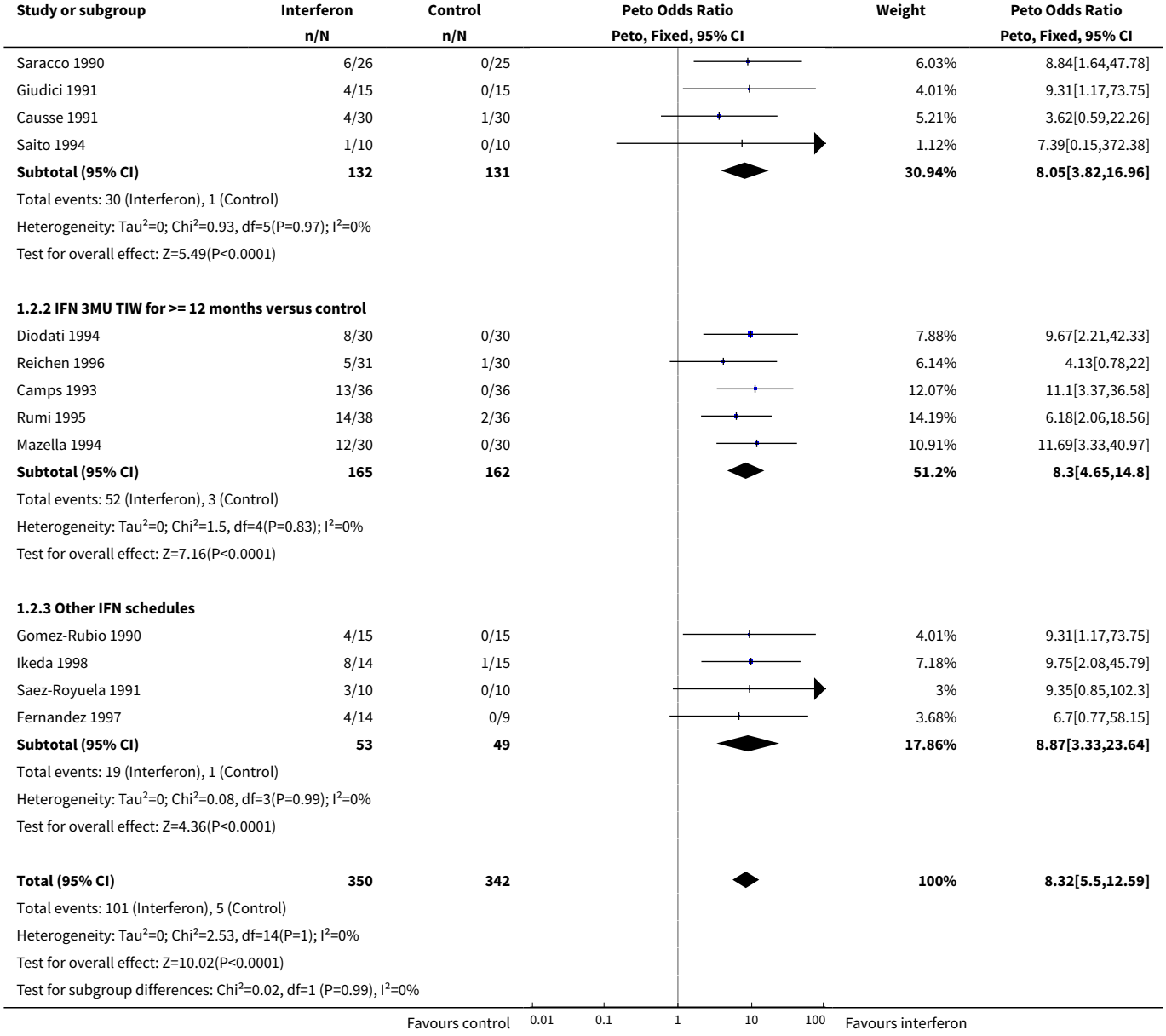


Study or subgroup	Interferon n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Davis 1989	22/58	2/51		11.3%	7.12[2.88,17.57]
Marcellin 1991	7/18	0/18		3.48%	11.18[2.19,56.91]
Saracco 1990	12/26	0/25		5.62%	12.36[3.43,44.54]
Causse 1991	13/30	2/30		6.87%	6.84[2.15,21.8]
Saito 1994	4/10	0/10		2.02%	10.75[1.27,91]
Giudici 1991	11/15	0/15		4.33%	21.17[4.92,91.18]
Cimino 1991	17/33	0/33		7.7%	14.2[4.75,42.44]
Subtotal (95% CI)	**190**	**182**		**41.33%**	**10.3[6.42,16.52]**
Total events: 86 (Interferon), 4 (Control)					
Heterogeneity: Tau²=0; Chi²=2.48, df=6(P=0.87); I²=0%					
Test for overall effect: Z=9.67(P<0.0001)					
1.1.2 IFN 3 MU TIW for >= 12 months versus control					
Camps 1993	18/36	1/36		8.52%	10.99[3.88,31.13]
Rumi 1995	24/38	0/36		9.87%	17.17[6.53,45.17]
Makris 1991	3/10	0/8		1.57%	7.69[0.68,86.86]
Reichen 1996	10/31	2/30		5.89%	4.92[1.41,17.21]
Mazella 1994	16/30	0/30		7.17%	14.61[4.7,45.45]
Diodati 1994	14/30	1/30		6.87%	9.7[3.05,30.92]
Subtotal (95% CI)	**175**	**170**		**39.88%**	**11.07[6.84,17.91]**
Total events: 85 (Interferon), 4 (Control)					
Heterogeneity: Tau²=0; Chi²=2.77, df=5(P=0.74); I²=0%					
Test for overall effect: Z=9.8(P<0.0001)					
1.1.3 Other IFN schedules					
Weiland 1990	11/21	0/12		4.2%	9.83[2.23,43.26]
Gomez-Rubio 1990	6/15	1/15		3.33%	6.06[1.15,31.97]
Capra 1993	12/21	0/19		5.16%	14.2[3.73,54.07]
Saez-Royuela 1991	5/10	1/10		2.66%	6.11[0.95,39.4]
Fernandez 1997	10/14	1/9		3.43%	10.1[1.96,52.02]
Subtotal (95% CI)	**81**	**65**		**18.79%**	**9.38[4.65,18.9]**
Total events: 44 (Interferon), 3 (Control)					
Heterogeneity: Tau²=0; Chi²=0.85, df=4(P=0.93); I²=0%					
Test for overall effect: Z=6.26(P<0.0001)					
Total (95% CI)	**446**	**417**		**100%**	**10.42[7.69,14.11]**
Total events: 215 (Interferon), 11 (Control)					
Heterogeneity: Tau²=0; Chi²=6.25, df=17(P=0.99); I²=0%					
Test for overall effect: Z=15.12(P<0.0001)					
Test for subgroup differences: Chi²=0.15, df=1 (P=0.93), I²=0%					

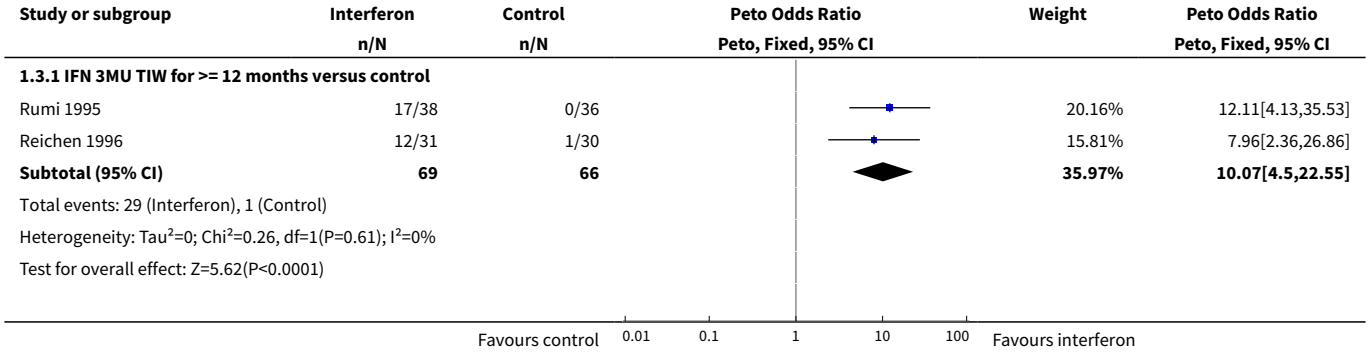
Analysis 1.2. Comparison 1 Interferon vs. control, Outcome 2 Biochemical SR.

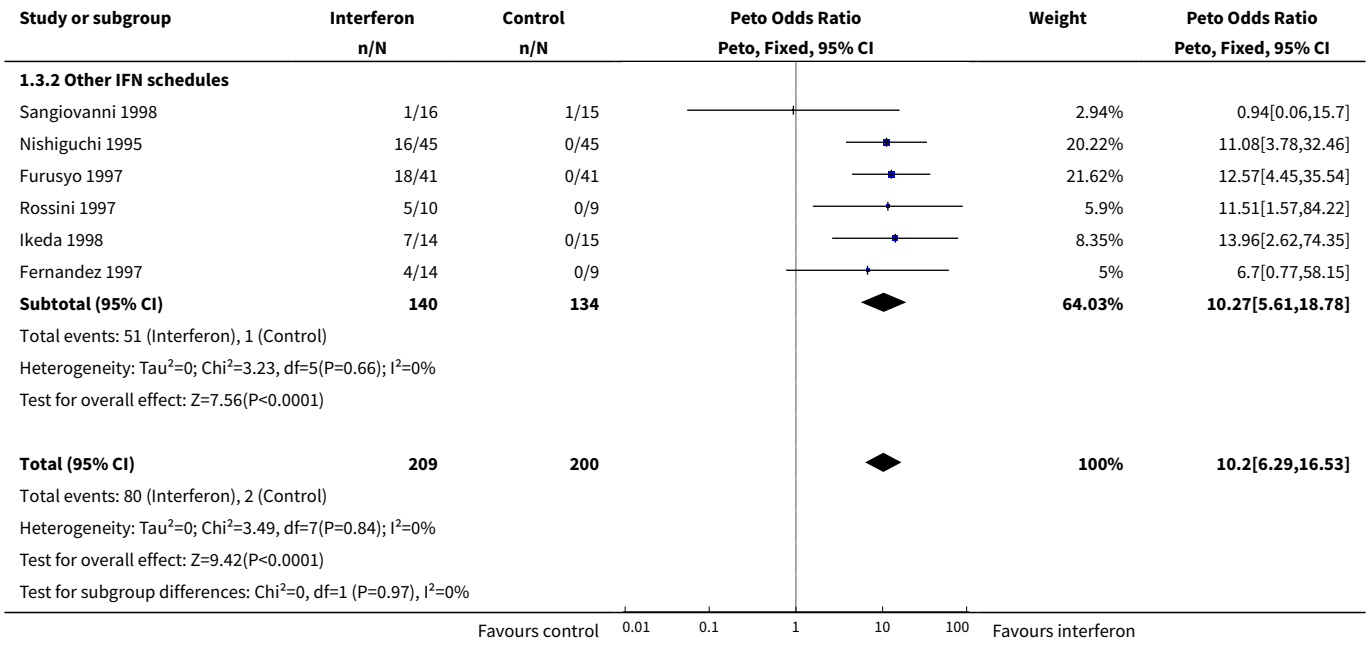


Study or subgroup	Interferon n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.2.1 IFN 3 MU TIW for 6 months versus control					
Cimino 1991	10/33	0/33		9.63%	10.19[2.68,38.74]
Marcellin 1991	5/18	0/18		4.95%	9.56[1.48,61.61]

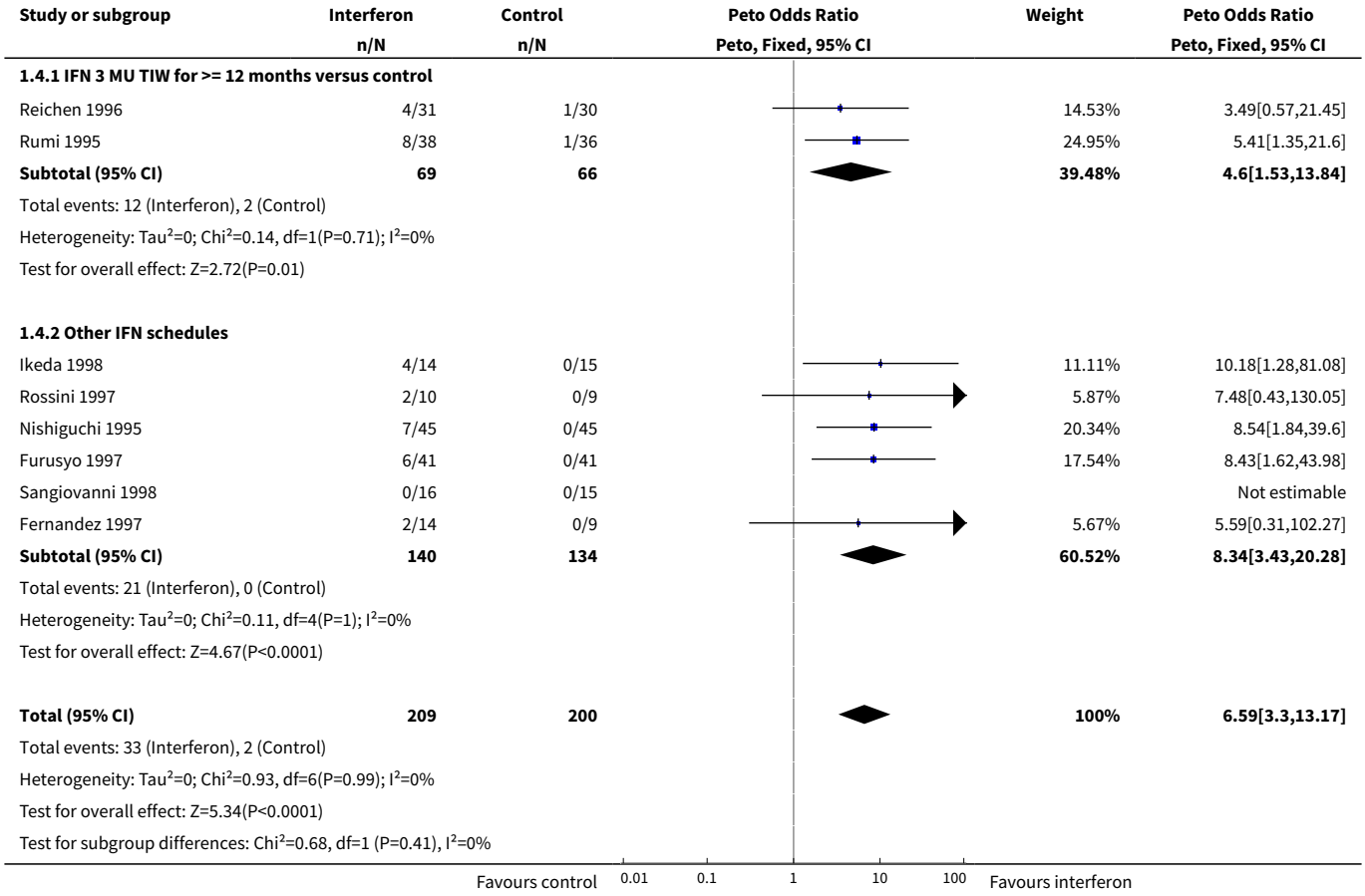


Analysis 1.3. Comparison 1 Interferon vs. control, Outcome 3 Virologic ETR.

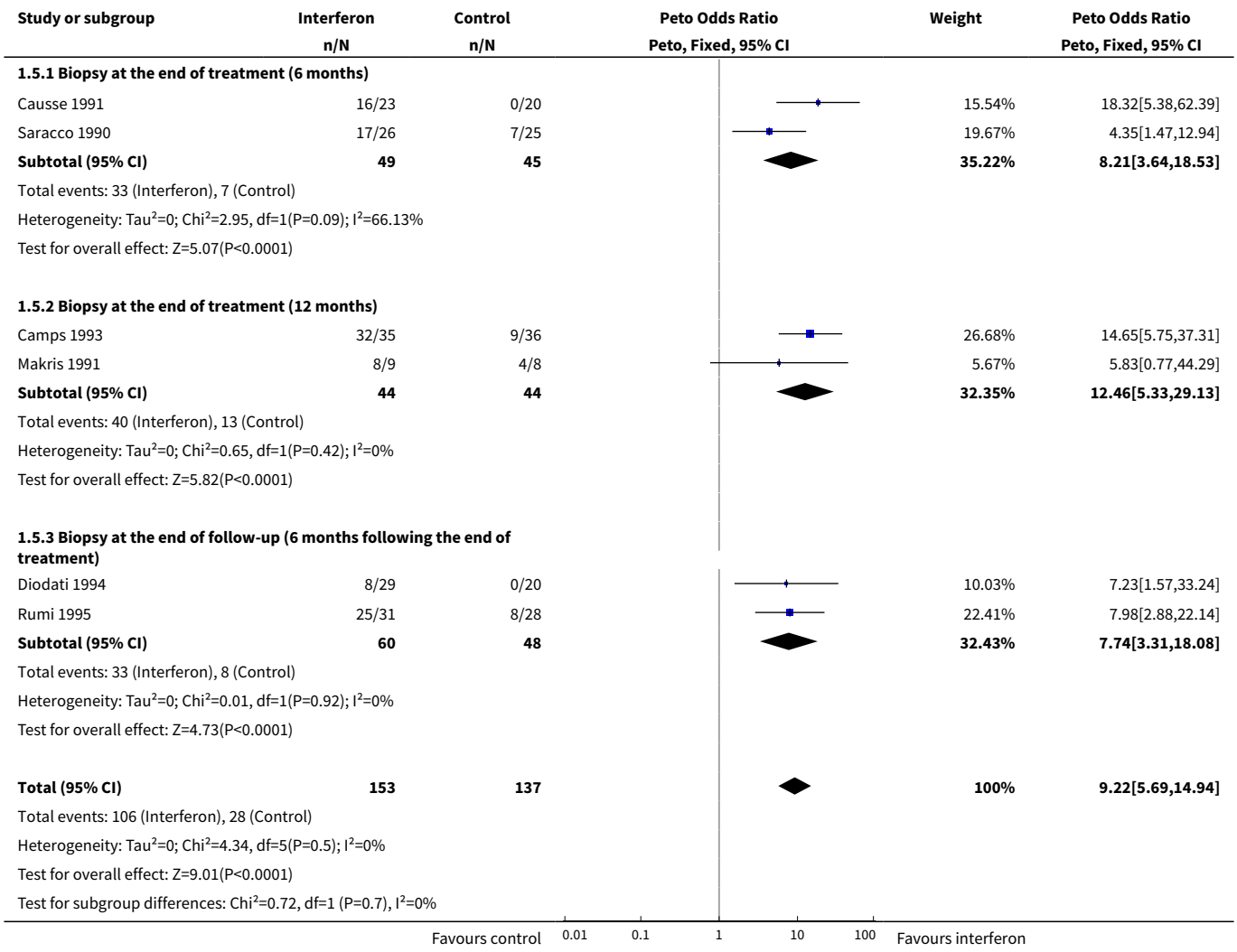




Analysis 1.4. Comparison 1 Interferon vs. control, Outcome 4 Virologic SR.



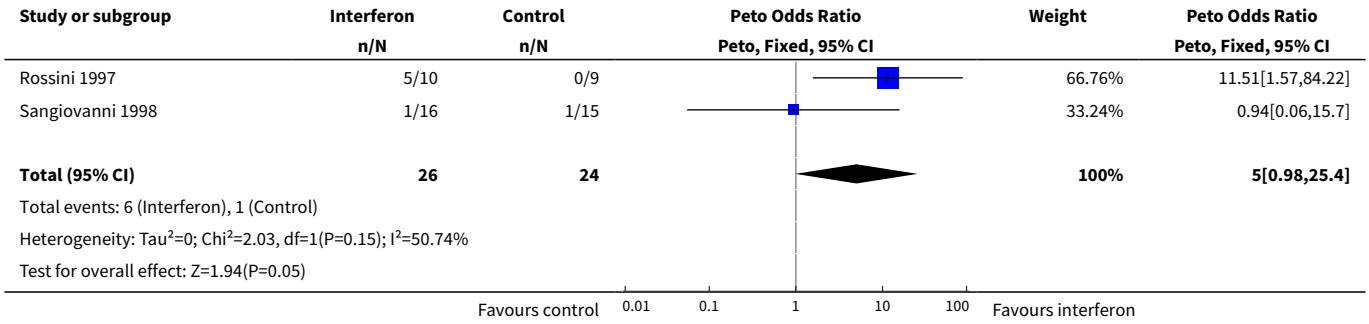
Analysis 1.5. Comparison 1 Interferon vs. control, Outcome 5 Improvement in liver histology.



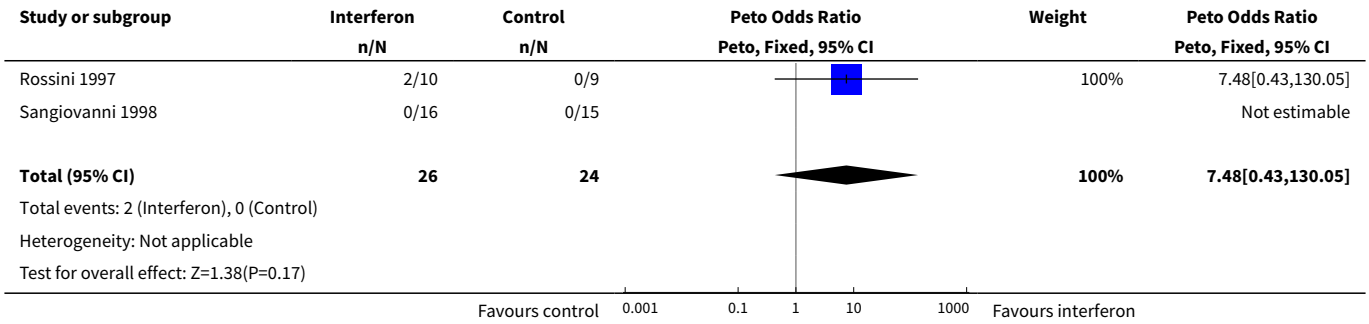
Comparison 2. Effect in patients with normal aminotransferases

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Virologic ETR	2	50	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.00 [0.98, 25.40]
2 Virologic SR	2	50	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.48 [0.43, 130.05]

Analysis 2.1. Comparison 2 Effect in patients with normal aminotransferases, Outcome 1 Virologic ETR.



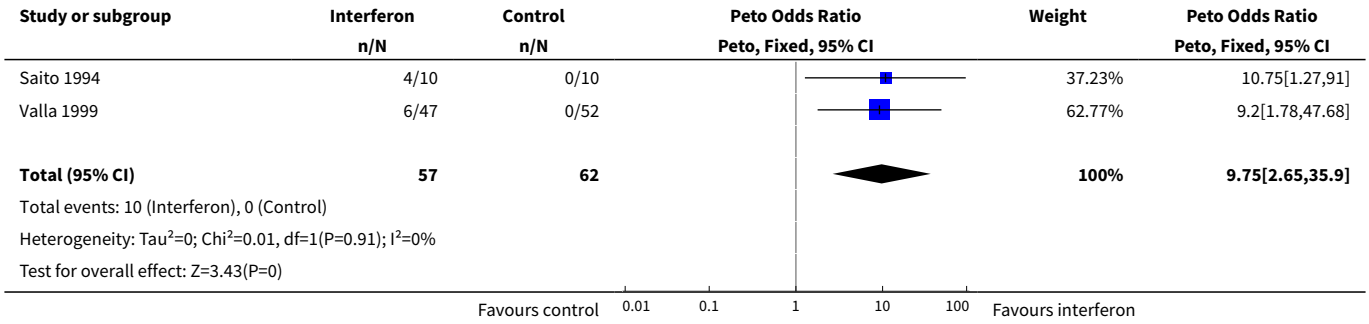
Analysis 2.2. Comparison 2 Effect in patients with normal aminotransferases, Outcome 2 Virologic SR.



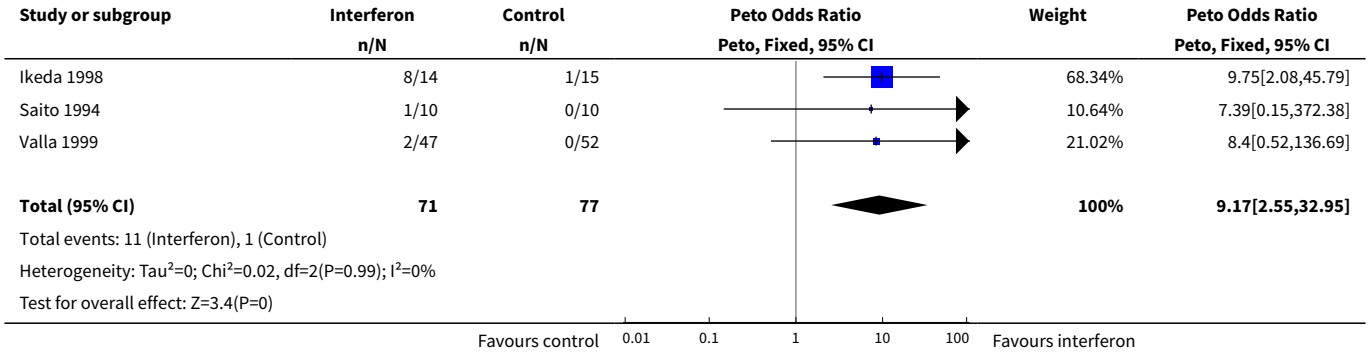
Comparison 3. Effect in cirrhotic patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Biochemical ETR	2	119	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.75 [2.65, 35.90]
2 Biochemical SR	3	148	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.17 [2.55, 32.95]
3 Virologic ETR	3	201	Peto Odds Ratio (Peto, Fixed, 95% CI)	12.16 [6.15, 24.05]
4 Virologic SR	3	201	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.84 [3.29, 23.77]
5 Hepatocellular carcinoma	3	218	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.38, 1.47]
6 Hepatocellular carcinoma (excluding Nishiguchi trial)	2	128	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.50 [0.21, 1.21]

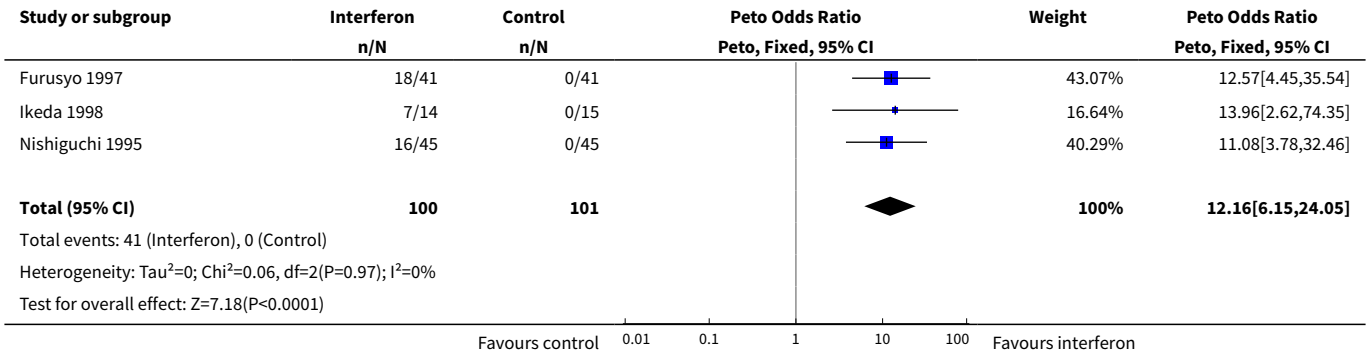
Analysis 3.1. Comparison 3 Effect in cirrhotic patients, Outcome 1 Biochemical ETR.



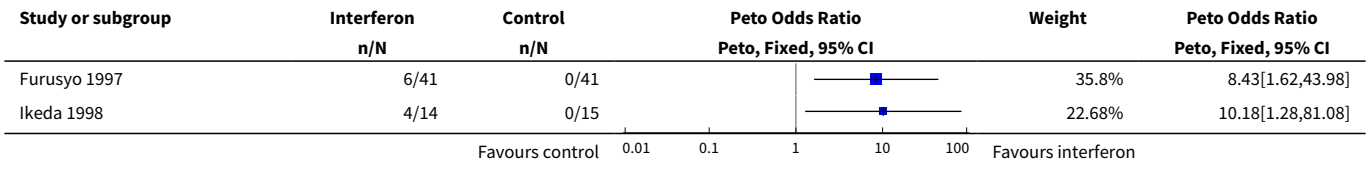
Analysis 3.2. Comparison 3 Effect in cirrhotic patients, Outcome 2 Biochemical SR.

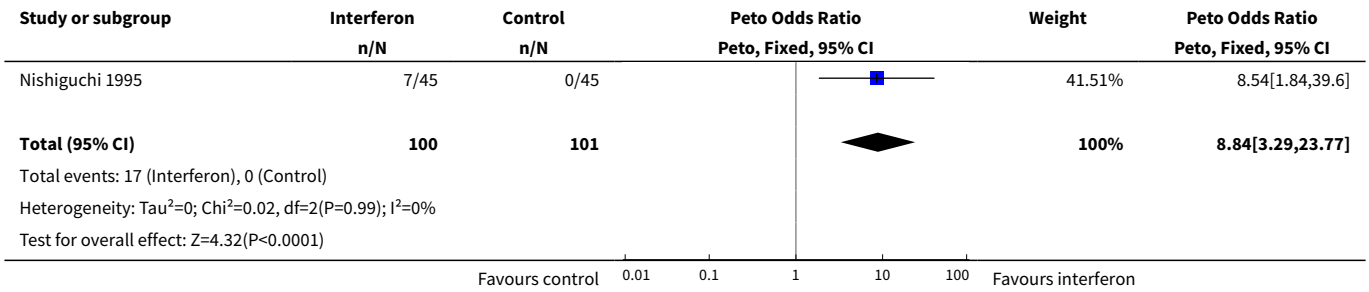


Analysis 3.3. Comparison 3 Effect in cirrhotic patients, Outcome 3 Virologic ETR.

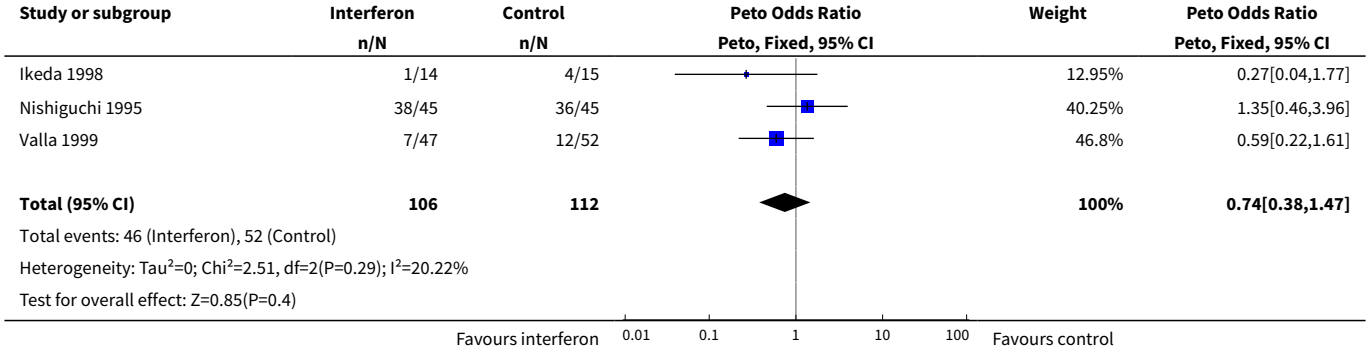


Analysis 3.4. Comparison 3 Effect in cirrhotic patients, Outcome 4 Virologic SR.

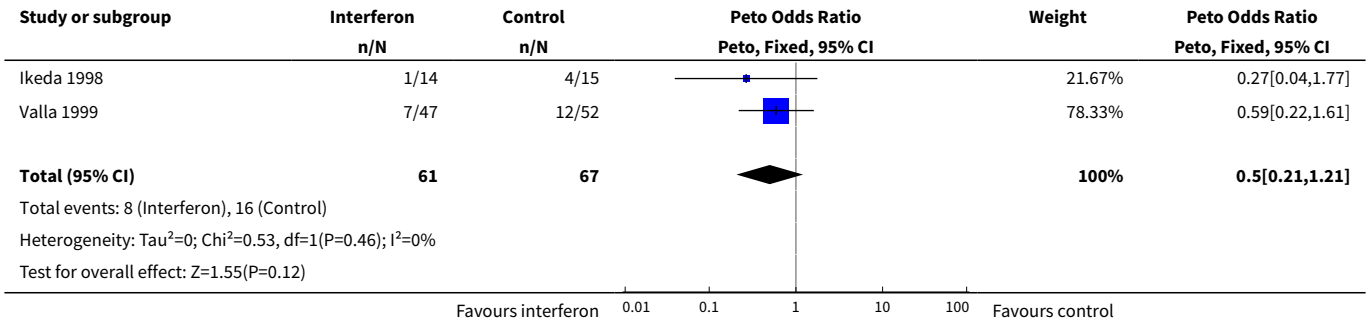




Analysis 3.5. Comparison 3 Effect in cirrhotic patients, Outcome 5 Hepatocellular carcinoma.



Analysis 3.6. Comparison 3 Effect in cirrhotic patients, Outcome 6 Hepatocellular carcinoma (excluding Nishiguchi trial).



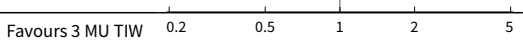
Comparison 4. Dose effect of interferon

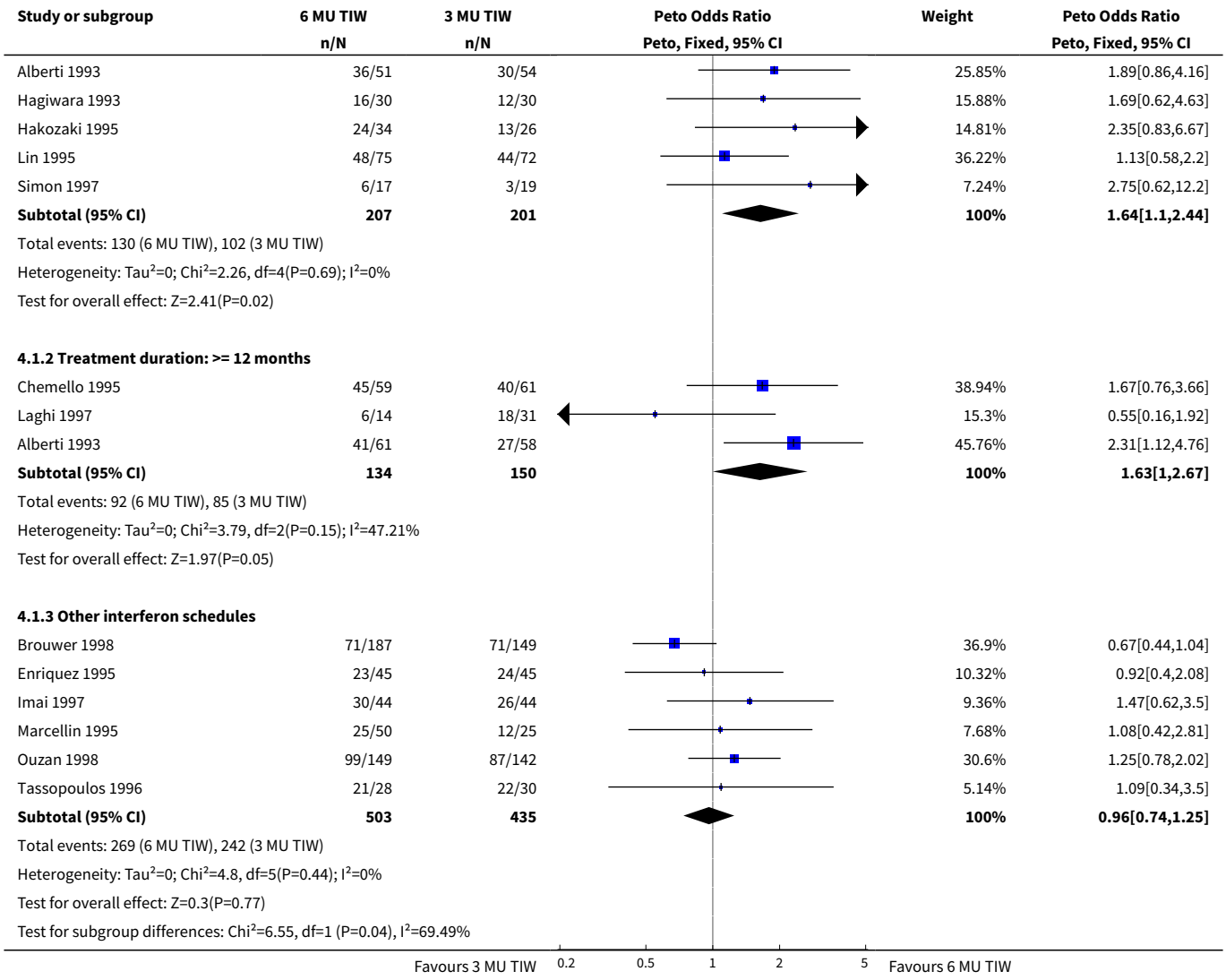
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Biochemical ETR	13		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 Treatment duration: 6 months	5	408	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.64 [1.10, 2.44]
1.2 Treatment duration: >= 12 months	3	284	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.63 [1.00, 2.67]
1.3 Other interferon schedules	6	938	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.74, 1.25]
2 Biochemical SR	15		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Treatment duration: 6 months	6	428	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.03 [1.27, 3.23]
2.2 Treatment duration: >= 12 months	4	302	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.08 [1.30, 3.34]
2.3 Other interferon schedules	7	962	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [1.10, 2.05]
3 Virologic ETR	8		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Treatment duration: 6 months	3	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.23 [1.13, 4.41]
3.2 Treatment duration: >= 12 months	3	183	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.79 [1.53, 5.09]
3.3 Other interferon schedules	3	659	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [1.06, 1.98]
4 Virologic SR	8		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Treatment duration: 6 months	3	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.69 [1.24, 5.84]
4.2 Treatment duration: >= 12 months	2	138	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.21 [1.10, 4.45]
4.3 Other interferon schedules	4	747	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.39 [0.98, 1.97]

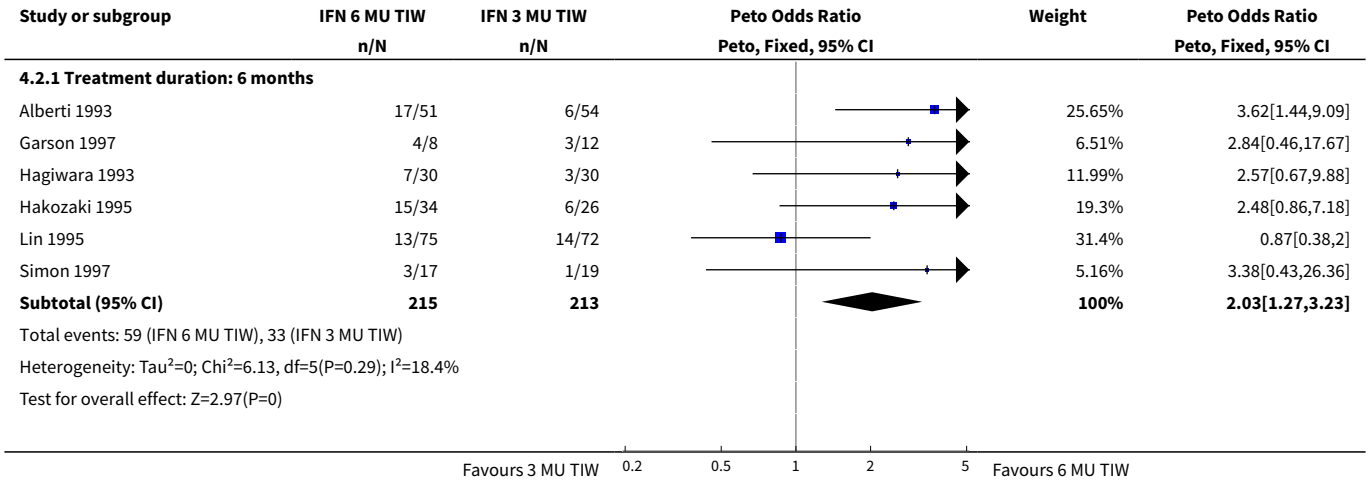
Analysis 4.1. Comparison 4 Dose effect of interferon, Outcome 1 Biochemical ETR.

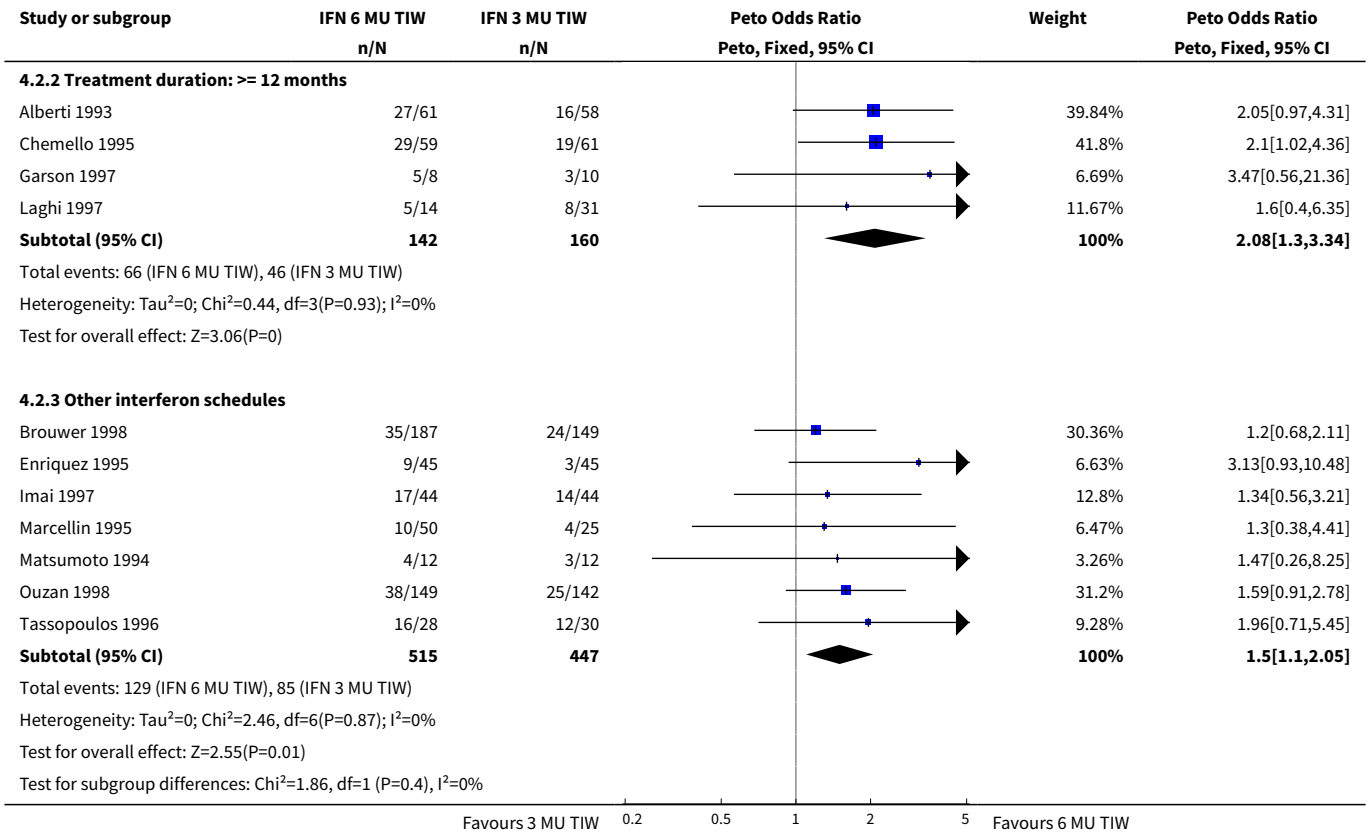
Study or subgroup	6 MU TIW n/N	3 MU TIW n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
4.1.1 Treatment duration: 6 months					



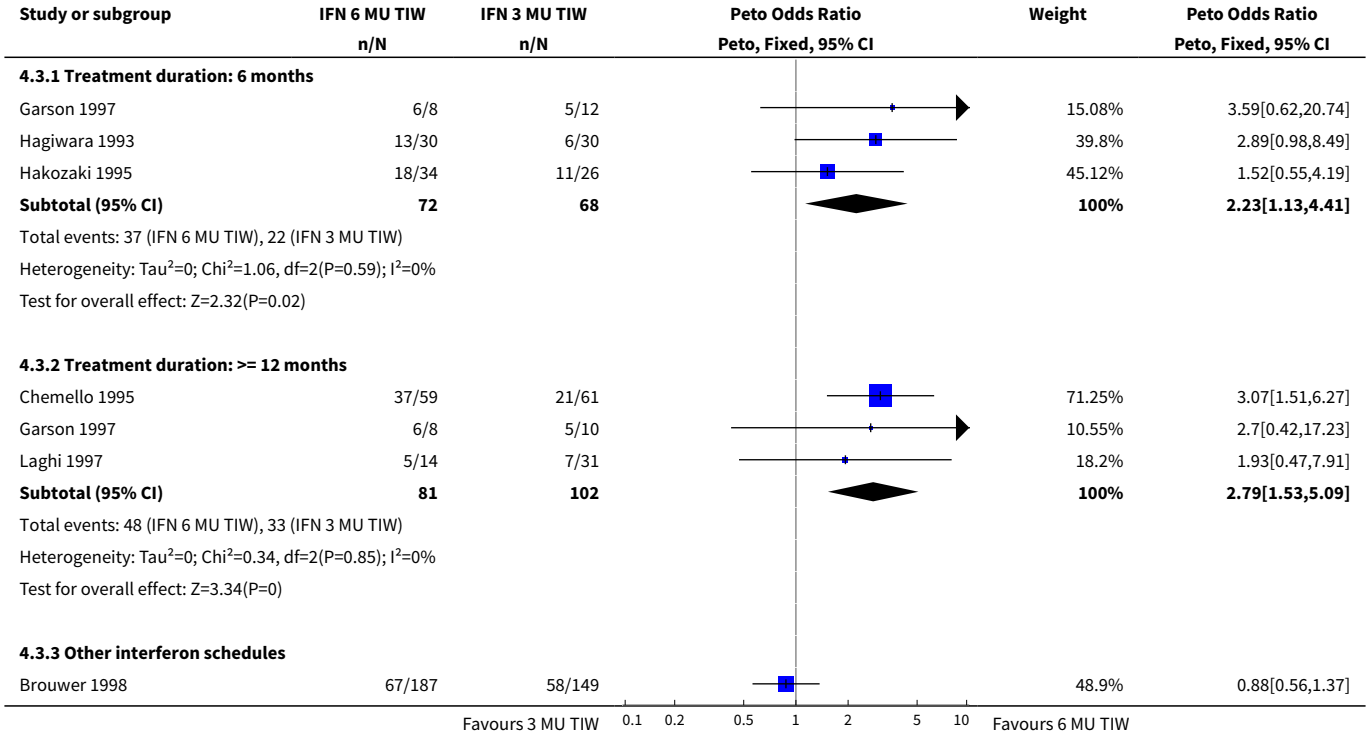


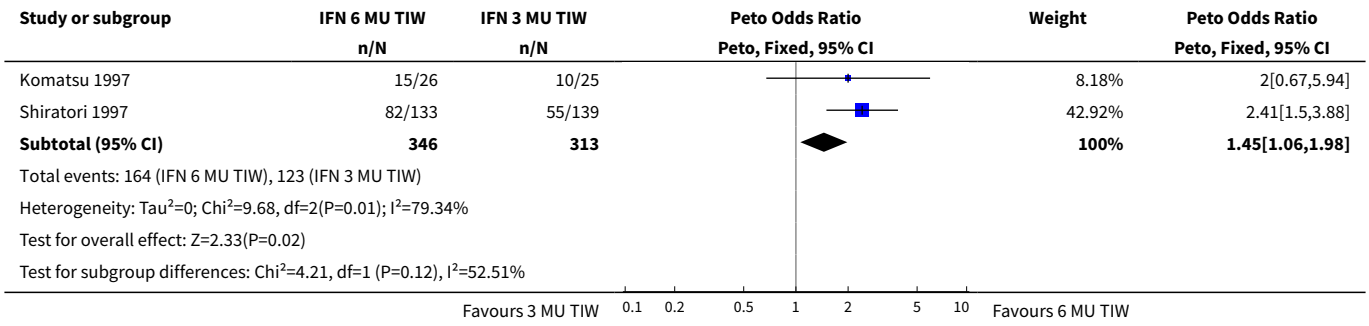
Analysis 4.2. Comparison 4 Dose effect of interferon, Outcome 2 Biochemical SR.



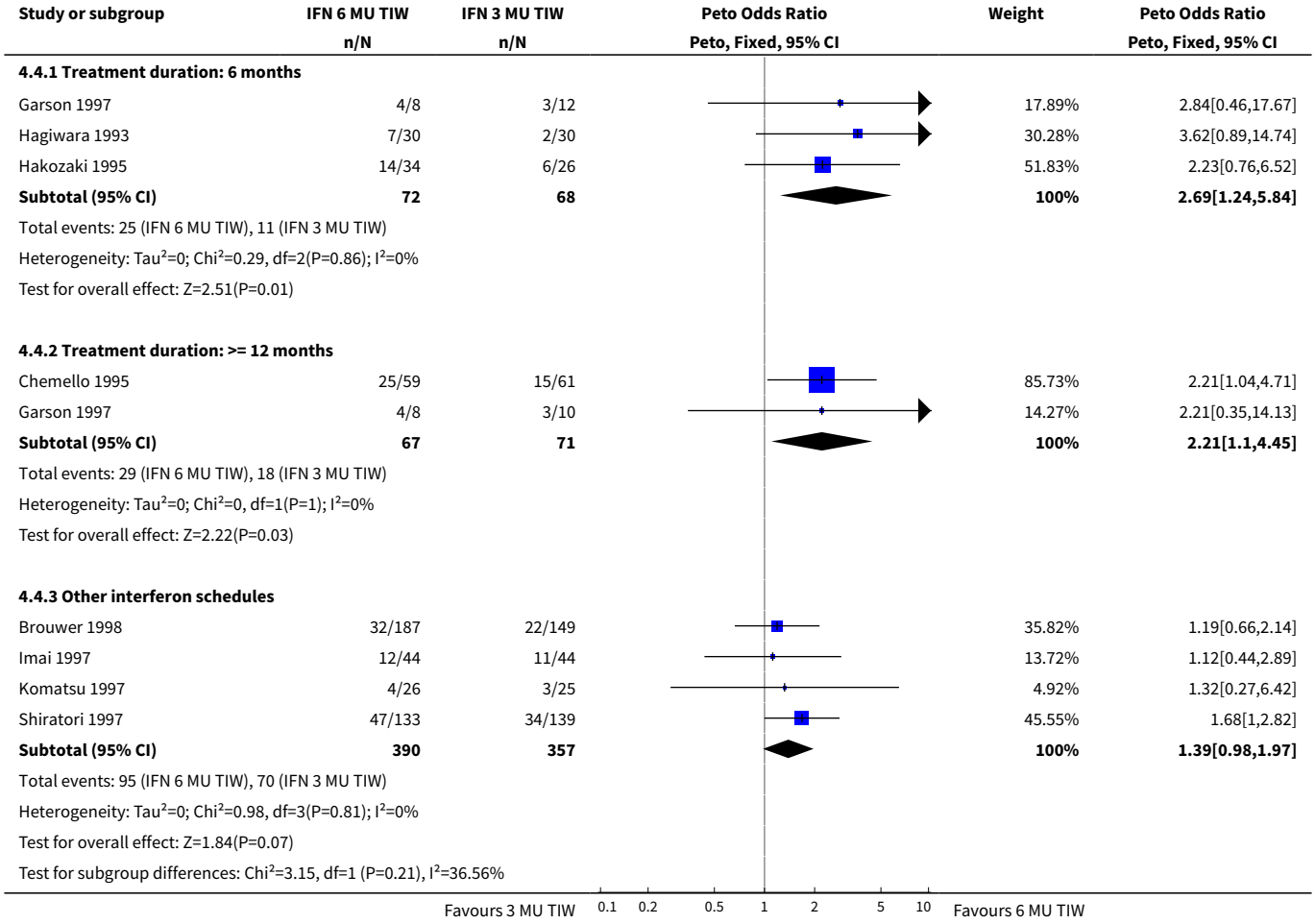


Analysis 4.3. Comparison 4 Dose effect of interferon, Outcome 3 Virologic ETR.





Analysis 4.4. Comparison 4 Dose effect of interferon, Outcome 4 Virologic SR.

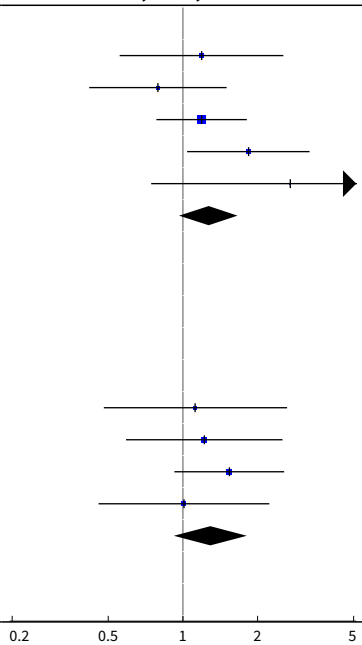


Comparison 5. Duration effect of interferon

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Biochemical ETR	9	1533	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [1.03, 1.57]
1.1 IFN 3 MU TIW	5	961	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.96, 1.66]
1.2 IFN 6 MU TIW	4	572	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.29 [0.92, 1.81]
2 Biochemical SR	10	1570	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.37 [1.83, 3.07]
2.1 IFN 3 MU TIW	6	983	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.51 [1.79, 3.52]
2.2 IFN 6 MU TIW	5	587	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.18 [1.46, 3.25]
3 Virologic ETR	3	610	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.62, 1.24]
3.1 IFN 3 MU TIW	2	478	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.55, 1.22]
3.2 IFN 6 MU TIW	2	132	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.54, 2.13]
4 Virologic SR	5	1056	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [1.30, 2.67]
4.1 IFN 3 MU TIW	3	680	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.12 [1.31, 3.44]
4.2 IFN 6 MU TIW	3	376	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.60 [0.94, 2.73]

Analysis 5.1. Comparison 5 Duration effect of interferon, Outcome 1 Biochemical ETR.

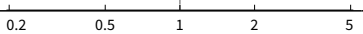
Study or subgroup	>= 12 months n/N	6 months n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
5.1.1 IFN 3 MU TIW					
Jouet 1994	25/56	21/52		7.76%	1.19[0.56,2.54]
Lin 1995	46/83	44/72		11.02%	0.79[0.42,1.5]
McHutchison 1998	62/225	56/231		25.55%	1.19[0.78,1.81]
Poynard 1995	46/103	30/99		13.88%	1.84[1.04,3.24]
Saracco 1993	10/14	12/26		2.69%	2.71[0.75,9.83]
Subtotal (95% CI)	**481**	**480**		**60.9%**	**1.27[0.96,1.66]**
Total events: 189 (>= 12 months), 163 (6 months)					
Heterogeneity: Tau^2=0; Chi^2=5.17, df=4(P=0.27); I^2=22.68%					
Test for overall effect: Z=1.7(P=0.09)					
5.1.2 IFN 6 MU TIW					
Chemello 1995	45/59	40/54		6.18%	1.12[0.48,2.63]
Craxi 1996	28/56	27/60		8.49%	1.22[0.59,2.52]
Degos 1998	57/124	43/121		17.32%	1.54[0.92,2.56]
Kasahara 1995	27/48	28/50		7.1%	1.01[0.46,2.23]
Subtotal (95% CI)	**287**	**285**		**39.1%**	**1.29[0.92,1.81]**
Total events: 157 (>= 12 months), 138 (6 months)					
Heterogeneity: Tau^2=0; Chi^2=0.94, df=3(P=0.81); I^2=0%					



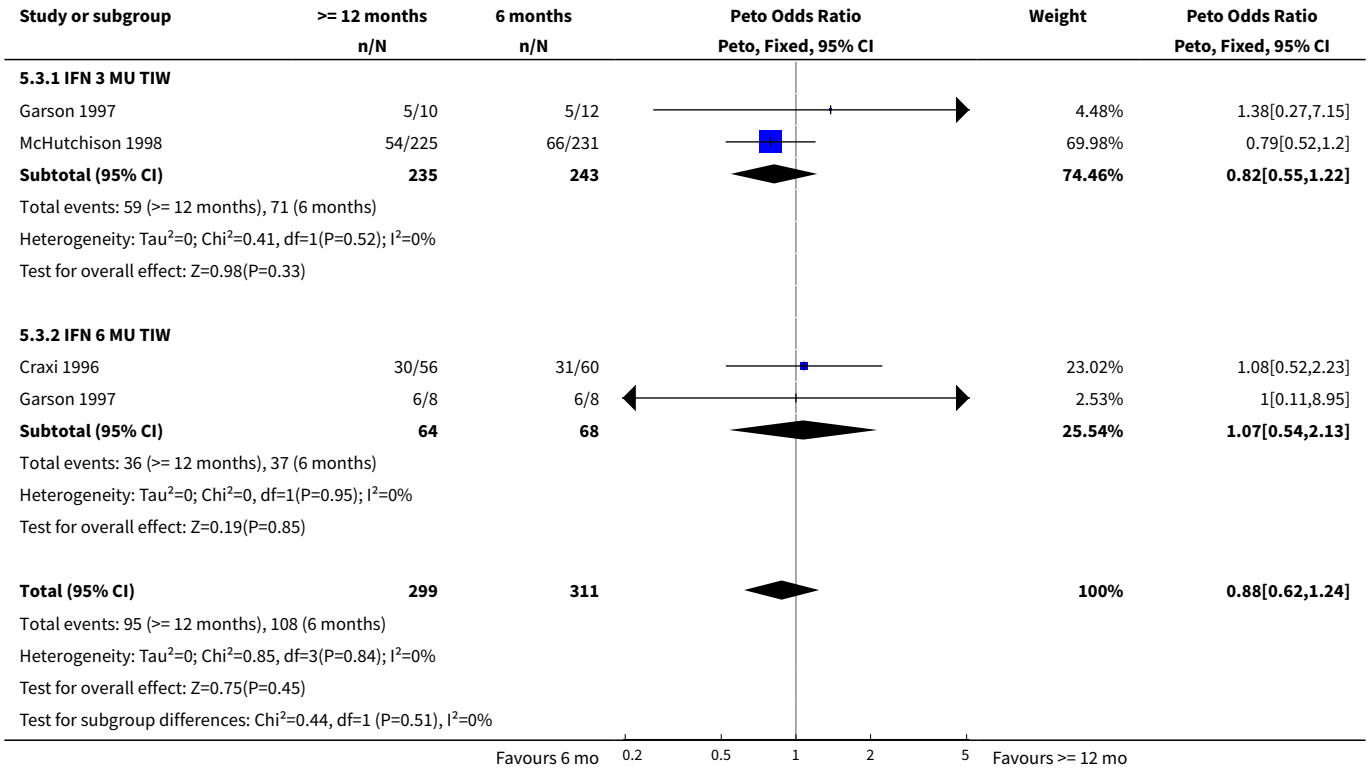
Study or subgroup	>= 12 months n/N	6 months n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Test for overall effect: Z=1.47(P=0.14)					
Total (95% CI)	**768**	**765**		**100%**	**1.27[1.03,1.57]**
Total events: 346 (>= 12 months), 301 (6 months)					
Heterogeneity: Tau^2=0; Chi^2=6.13, df=8(P=0.63); I^2=0%					
Test for overall effect: Z=2.25(P=0.02)					
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.93), I^2=0%					

Analysis 5.2. Comparison 5 Duration effect of interferon, Outcome 2 Biochemical SR.

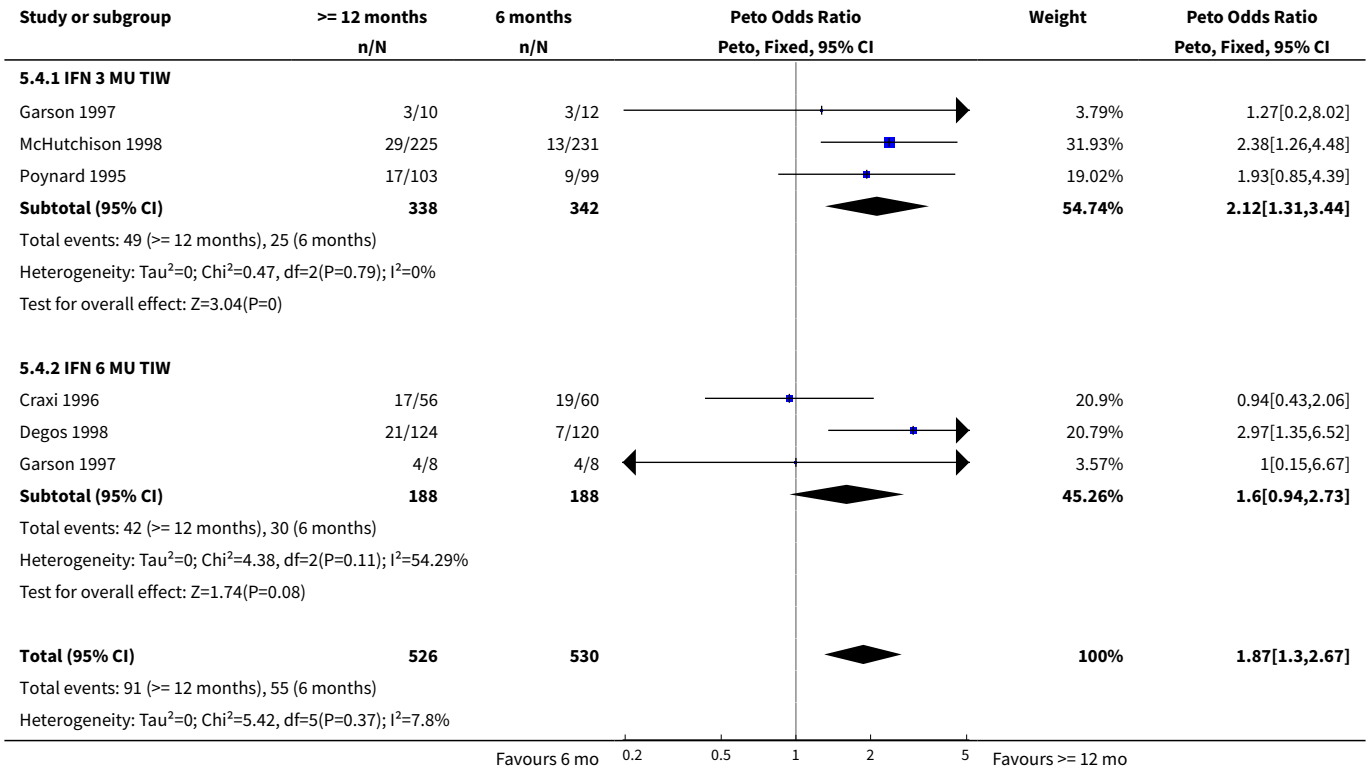
Study or subgroup	>=12 months n/N	6 months n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
5.2.1 IFN 3 MU TIW					
Garson 1997	3/10	3/12		1.96%	1.27[0.2,8.02]
Jouet 1994	16/56	7/52		7.9%	2.44[0.98,6.12]
Lin 1995	27/83	14/72		13.07%	1.95[0.96,3.98]
McHutchison 1998	38/225	17/231		20.98%	2.45[1.4,4.3]
Poynard 1995	23/103	8/99		11.41%	2.98[1.39,6.39]
Saracco 1993	8/14	4/26		3.39%	6.95[1.71,28.18]
Subtotal (95% CI)	**491**	**492**		**58.71%**	**2.51[1.79,3.52]**
Total events: 115 (>=12 months), 53 (6 months)					
Heterogeneity: Tau^2=0; Chi^2=3.24, df=5(P=0.66); I^2=0%					
Test for overall effect: Z=5.37(P<0.0001)					
5.2.2 IFN 6 MU TIW					
Chemello 1995	29/59	15/54		11.71%	2.44[1.15,5.18]
Craxi 1996	10/56	11/60		7.5%	0.97[0.38,2.48]
Degos 1998	21/124	5/120		10.09%	3.8[1.69,8.56]
Garson 1997	5/8	4/8		1.82%	1.61[0.24,10.9]
Kasahara 1995	23/48	15/50		10.17%	2.11[0.94,4.74]
Subtotal (95% CI)	**295**	**292**		**41.29%**	**2.18[1.46,3.25]**
Total events: 88 (>=12 months), 50 (6 months)					
Heterogeneity: Tau^2=0; Chi^2=4.84, df=4(P=0.3); I^2=17.39%					
Test for overall effect: Z=3.8(P=0)					
Total (95% CI)	**786**	**784**		**100%**	**2.37[1.83,3.07]**
Total events: 203 (>=12 months), 103 (6 months)					
Heterogeneity: Tau^2=0; Chi^2=8.37, df=10(P=0.59); I^2=0%					
Test for overall effect: Z=6.55(P<0.0001)					
Test for subgroup differences: Chi^2=0.29, df=1 (P=0.59), I^2=0%					



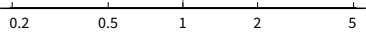
Analysis 5.3. Comparison 5 Duration effect of interferon, Outcome 3 Virologic ETR.



Analysis 5.4. Comparison 5 Duration effect of interferon, Outcome 4 Virologic SR.



Study or subgroup	>= 12 months n/N	6 months n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Test for overall effect: Z=3.42(P=0)					
Test for subgroup differences: Chi²=0.58, df=1 (P=0.45), I²=0%					

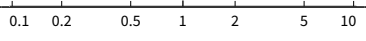


Comparison 6. Effect of different formulations of interferon

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Biochemical ETR	6	2330	Odds Ratio (M-H, Random, 95% CI)	1.39 [0.84, 2.30]
2 Biochemical SR	6	2330	Odds Ratio (M-H, Random, 95% CI)	1.58 [0.81, 3.10]
3 Virologic ETR	6	2330	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.76, 2.68]
4 Virologic SR	6	2330	Odds Ratio (M-H, Random, 95% CI)	1.41 [0.67, 2.97]

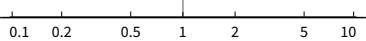
Analysis 6.1. Comparison 6 Effect of different formulations of interferon, Outcome 1 Biochemical ETR.

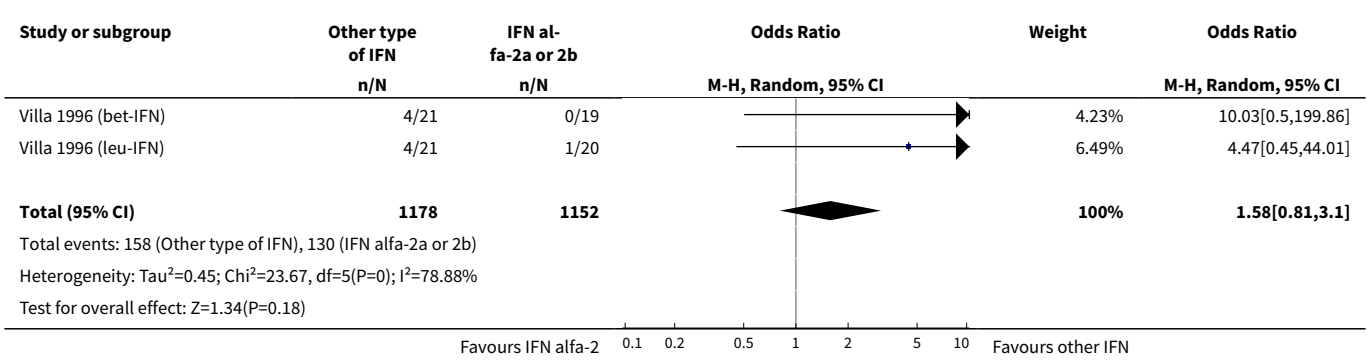
Study or subgroup	Other type of IFN n/N	IFN alfa-2a or 2b n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Farrell 1998	204/538	188/533		24.74%	1.12[0.87,1.44]
Rumi 1996	23/118	26/116		18.63%	0.84[0.45,1.57]
Tong 1997 (CIFN 3µg)	79/240	35/232		21.77%	2.76[1.76,4.33]
Tong 1997 (CIFN 9µg)	79/240	88/232		22.93%	0.8[0.55,1.17]
Villa 1996 (bet-IFN)	9/21	0/19		2.65%	29.64[1.58,555.72]
Villa 1996 (leu-IFN)	9/21	5/20		9.27%	2.25[0.59,8.52]
Total (95% CI)	**1178**	**1152**		**100%**	**1.39[0.84,2.3]**
Total events: 403 (Other type of IFN), 342 (IFN alfa-2a or 2b)					
Heterogeneity: Tau²=0.25; Chi²=24.66, df=5(P=0); I²=79.72%					
Test for overall effect: Z=1.29(P=0.2)					



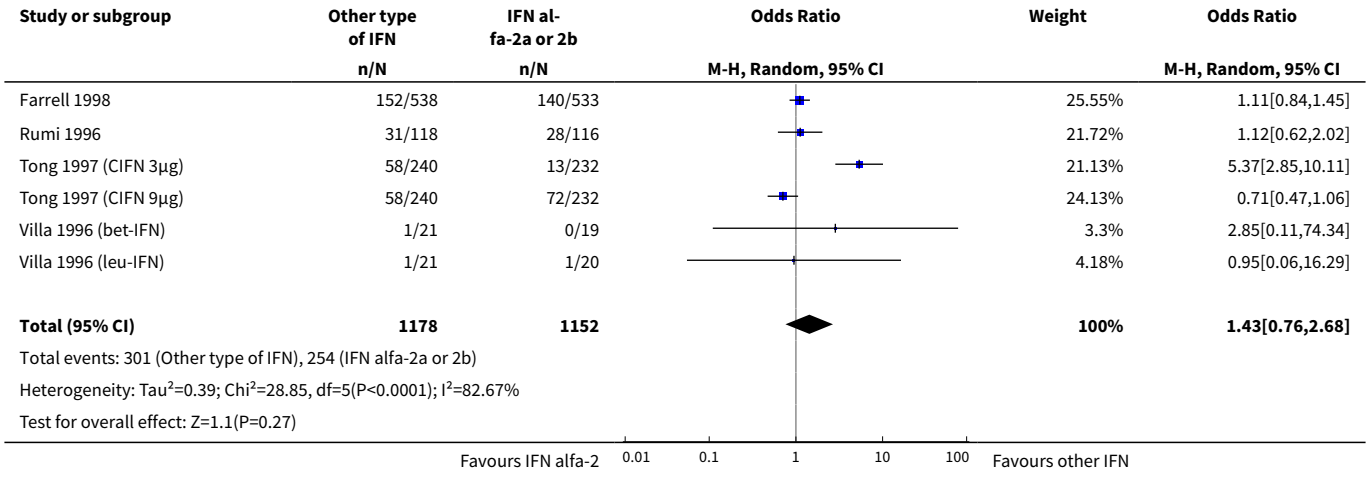
Analysis 6.2. Comparison 6 Effect of different formulations of interferon, Outcome 2 Biochemical SR.

Study or subgroup	Other type of IFN n/N	IFN alfa-2a or 2b n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Farrell 1998	36/538	55/533		23.61%	0.62[0.4,0.97]
Rumi 1996	36/118	22/116		21.61%	1.88[1.02,3.44]
Tong 1997 (CIFN 3µg)	39/240	13/232		20.99%	3.27[1.7,6.3]
Tong 1997 (CIFN 9µg)	39/240	39/232		23.08%	0.96[0.59,1.56]

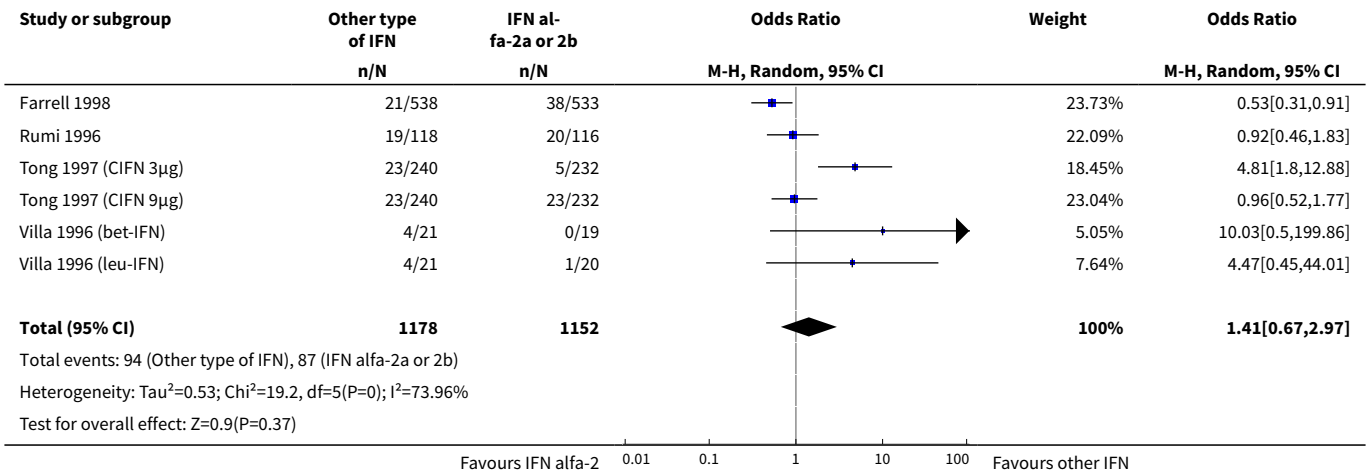




Analysis 6.3. Comparison 6 Effect of different formulations of interferon, Outcome 3 Virologic ETR.



Analysis 6.4. Comparison 6 Effect of different formulations of interferon, Outcome 4 Virologic SR.



Comparison 7. Effect of tailored regimen vs. fixed-dose regimen

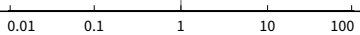
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Biochemical ETR	2	401	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.78 [0.52, 1.16]
2 Biochemical SR	2	401	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.71, 1.98]
3 Virologic ETR	2	401	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.62, 1.39]
4 Virologic SR	2	401	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.72, 2.09]

Analysis 7.1. Comparison 7 Effect of tailored regimen vs. fixed-dose regimen, Outcome 1 Biochemical ETR.

Study or subgroup	Tailored n/N	Fixed-dose n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Brouwer 1998	71/187	71/149		83.89%	0.67[0.44,1.04]
Reichen 1996	15/34	10/31		16.11%	1.64[0.61,4.42]
Total (95% CI)	**221**	**180**		**100%**	**0.78[0.52,1.16]**
Total events: 86 (Tailored), 81 (Fixed-dose)					
Heterogeneity: Tau^2=0; Chi^2=2.58, df=1(P=0.11); I^2=61.3%					
Test for overall effect: Z=1.24(P=0.21)					

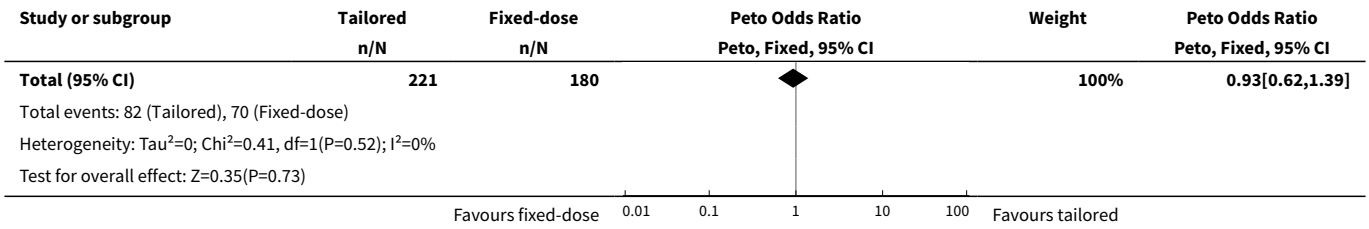
Analysis 7.2. Comparison 7 Effect of tailored regimen vs. fixed-dose regimen, Outcome 2 Biochemical SR.

Study or subgroup	Tailored n/N	Fixed-dose n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Brouwer 1998	35/187	24/149		83.87%	1.2[0.68,2.11]
Reichen 1996	6/34	5/31		16.13%	1.11[0.31,4.03]
Total (95% CI)	**221**	**180**		**100%**	**1.18[0.71,1.98]**
Total events: 41 (Tailored), 29 (Fixed-dose)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=0.64(P=0.52)					

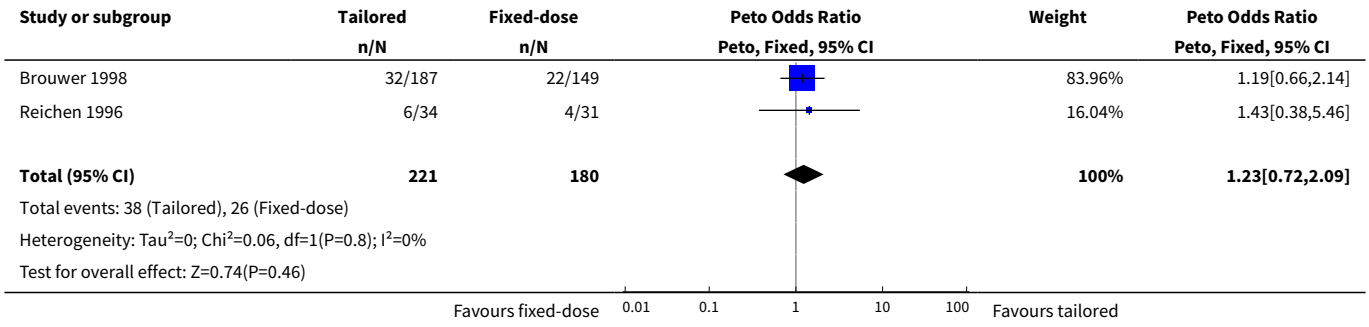


Analysis 7.3. Comparison 7 Effect of tailored regimen vs. fixed-dose regimen, Outcome 3 Virologic ETR.

Study or subgroup	Tailored n/N	Fixed-dose n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Brouwer 1998	67/187	58/149		82.93%	0.88[0.56,1.37]
Reichen 1996	15/34	12/31		17.07%	1.25[0.47,3.32]



Analysis 7.4. Comparison 7 Effect of tailored regimen vs. fixed-dose regimen, Outcome 4 Virologic SR.

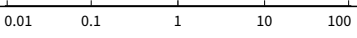


Comparison 8. Sensitivity analysis on allocation concealment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Biochemical ETR	18	863	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.42 [7.69, 14.11]
1.1 Adequate allocation concealment	4	274	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.88 [5.73, 17.02]
1.2 Unclear or indequate allocation concealment	14	589	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.67 [7.40, 15.39]
2 Biochemical SR	15	692	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.32 [5.50, 12.59]
2.1 Adequate allocation concealment	2	132	Peto Odds Ratio (Peto, Fixed, 95% CI)	11.37 [4.79, 26.99]
2.2 Unclear or inadequate allocation concealment	13	560	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.58 [4.73, 12.15]

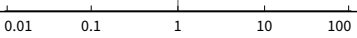
Analysis 8.1. Comparison 8 Sensitivity analysis on allocation concealment, Outcome 1 Biochemical ETR.

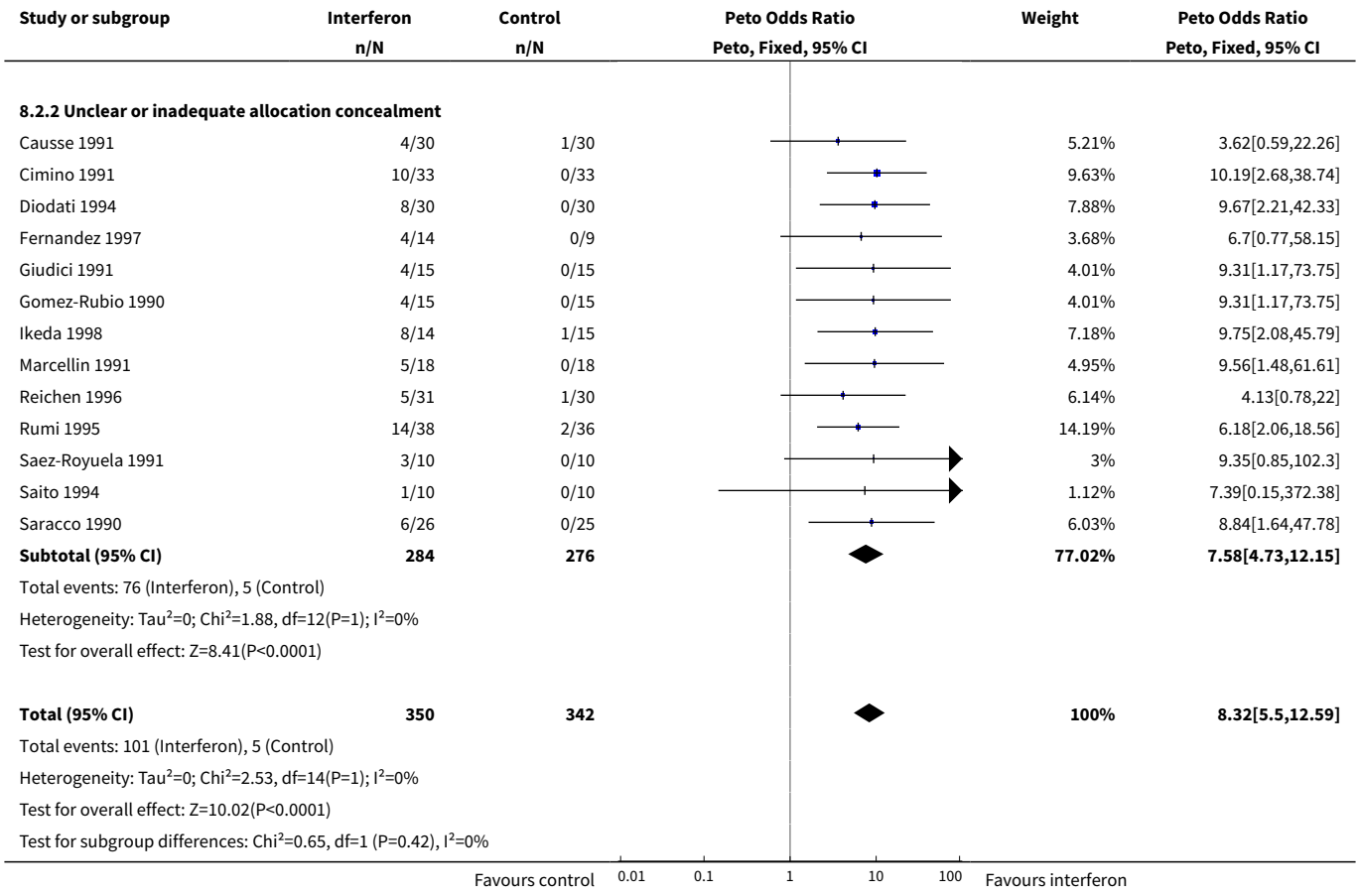
Study or subgroup	Interferon n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
8.1.1 Adequate allocation concealment					
Camps 1993	18/36	1/36		8.52%	10.99[3.88,31.13]
Davis 1989	22/58	2/51		11.3%	7.12[2.88,17.57]
Mazella 1994	16/30	0/30		7.17%	14.61[4.7,45.45]
Weiland 1990	11/21	0/12		4.2%	9.83[2.23,43.26]
Subtotal (95% CI)	**145**	**129**		**31.19%**	**9.88[5.73,17.02]**
Total events: 67 (Interferon), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1, df=3(P=0.8); I^2=0%					
Test for overall effect: Z=8.25(P<0.0001)					
8.1.2 Unclear or indequate allocation concealment					
Capra 1993	12/21	0/19		5.16%	14.2[3.73,54.07]
Causse 1991	13/30	2/30		6.87%	6.84[2.15,21.8]
Cimino 1991	17/33	0/33		7.7%	14.2[4.75,42.44]
Diodati 1994	14/30	1/30		6.87%	9.7[3.05,30.92]
Fernandez 1997	10/14	1/9		3.43%	10.1[1.96,52.02]
Giudici 1991	11/15	0/15		4.33%	21.17[4.92,91.18]
Gomez-Rubio 1990	6/15	1/15		3.33%	6.06[1.15,31.97]
Makris 1991	3/10	0/8		1.57%	7.69[0.68,86.86]
Marcellin 1991	7/18	0/18		3.48%	11.18[2.19,56.91]
Reichen 1996	10/31	2/30		5.89%	4.92[1.41,17.21]
Rumi 1995	24/38	0/36		9.87%	17.17[6.53,45.17]
Saez-Royuela 1991	5/10	1/10		2.66%	6.11[0.95,39.4]
Saito 1994	4/10	0/10		2.02%	10.75[1.27,91]
Saracco 1990	12/26	0/25		5.62%	12.36[3.43,44.54]
Subtotal (95% CI)	**301**	**288**		**68.81%**	**10.67[7.4,15.39]**
Total events: 148 (Interferon), 8 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.19, df=13(P=0.97); I^2=0%					
Test for overall effect: Z=12.67(P<0.0001)					
Total (95% CI)	**446**	**417**		**100%**	**10.42[7.69,14.11]**
Total events: 215 (Interferon), 11 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.25, df=17(P=0.99); I^2=0%					
Test for overall effect: Z=15.12(P<0.0001)					
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.82), I^2=0%					



Analysis 8.2. Comparison 8 Sensitivity analysis on allocation concealment, Outcome 2 Biochemical SR.

Study or subgroup	Interferon n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
8.2.1 Adequate allocation concealment					
Camps 1993	13/36	0/36		12.07%	11.1[3.37,36.58]
Mazella 1994	12/30	0/30		10.91%	11.69[3.33,40.97]
Subtotal (95% CI)	**66**	**66**		**22.98%**	**11.37[4.79,26.99]**
Total events: 25 (Interferon), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.95); I^2=0%					
Test for overall effect: Z=5.51(P<0.0001)					





WHAT'S NEW

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

CONTRIBUTIONS OF AUTHORS

CR, TT, VL, PM, PO, JPZ and TP wrote the first draft of the protocol and the review. TT, VL and TP performed the literature searches, and participated in the selection of trials and data extraction. TT and TP did the statistical analyses. RM verified the statistical analyses. RM, CR and TP rewrote the manuscript in light of the suggestions of the reviewers.

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 Welcome, and AMGEN.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Canadian Association for the Study of the Liver, Canada.
- Royal College of Physicians and Surgeons of Canada, Canada.
- Club Francophone de l'Hypertension Portale, France.
- Association Francaise pour l'Etude du Foie, France.
- Recherche et Partage, France.

NOTES

The protocol for this systematic Review was first published in The Cochrane Library, Issue 3, 1997 with the title 'Interferon for chronic hepatitis C'. It was prepared by Poynard T, Leroy V, Cohard M, Thevenot T, Mathurin P, Opolon P, Zarski JP.

Robert P. Myers became the leading author of the Review in 2001. Due to the fact that it was only intended to include interferon naive patients, the title has been changed into 'Interferon for interferon naive patients with chronic hepatitis C'.

Investigators involved in the included trials are invited to contact the authors to clarify methodological issues (particularly the methods of generating the allocation sequence, concealing allocation, and double-blinding) so that future versions of the review can be updated.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiviral Agents [*therapeutic use]; Hepatitis C, Chronic [*drug therapy]; Interferons [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans