Interferon alfa with or without ribavirin for chronic hepatitis C: systematic review of randomised trials

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Abstract

Objective To assess the efficacy and safety of interferon alfa with or without ribavirin for treatment of chronic hepatitis C.

Design Systematic review of randomised trials on interferon alfa plus ribavirin combination therapy versus interferon alfa. Patients were naive (not previously treated with interferon), relapsers (transient response to previous interferon therapy), or non-responders (no response to previous interferon therapy).

Studies reviewed Of 1155 references identified, 48 trials with 6585 patients met the inclusion criteria. Patients were followed to the end of treatment in 20 trials and in 28 trials for 12-96 weeks after treatment.

Main outcome measures Virological response and morbidity plus mortality.

Results Compared with interferon, combination therapy reduced the risk of not having a sustained virological response for 6 months by 26% in naive patients (relative risk 0.74, 95% confidence interval 0.70 to 0.78), 33% in relapsers (0.67, 0.57 to 0.78), and 11% in non-responders (0.89, 0.83 to 0.96). Morbidity and mortality showed a non-significant trend in favour of combination therapy (Peto odds ratio 0.45, 0.19 to 1.06). Combination therapy significantly reduced the risk of not having improvement in results of histology by 17% in naive patients (0.83, 0.74 to 0.93) and by 27% in relapsers and non-responders (0.73, 0.66 to 0.82). The risk of treatment discontinuations was significantly higher after combination therapy (1.28, 1.07 to 1.52).

Conclusion Treatment with interferon alfa plus ribavirin has a significant beneficial effect on the virological and histological responses of patients with chronic hepatitis C, irrespective of previous treatment. Combination therapy may therefore also be considered appropriate for relapsers and non-responders.

Introduction

In industrialised countries, chronic hepatitis C accounts for 40% of cases of end stage cirrhosis, 60% of cases of hepatocellular carcinoma, and 30% of liver transplants,[1] but the course of chronic hepatitis C is not completely understood. Only 0.4% of 1018 women infected with hepatitis C through rhesus immunisation developed cirrhosis over a period of 20 years[2], and only 6% of young adults infected with hepatitis C developed cirrhosis after 45 years.[3] Other studies suggest that histological signs of cirrhosis are present in 20% of patients with chronic hepatitis C within 20 years[4 5] and that once cirrhosis is established, hepatocellular carcinoma develops in 1-4% of affected patients per year.[5 6]

A meta-analysis showed that only about 17% of patients with chronic hepatitis C obtained a sustained virological response on interferon monotherapy, which was recommended treatment until the late 1990s.[7] At present, interferon alfa plus ribavirin is the recommended treatment for patients who are interferon naive, but its benefit in relapsers and non-responders has been questioned.[1] Furthermore, there is no clear evidence as to whether treatment reduces the risk of liver related morbidity or mortality.[8–10] We performed a systematic review to assess the efficacy and safety of interferon with or without ribavirin for naive patients, relapsers, and non-responders with chronic hepatitis C.

Methods

The study included trials in which patients with chronic hepatitis C were randomised to interferon alfa plus ribavirin versus interferon alfa. Inclusion was regardless of blinding, publication status, language, or intervention regimen.[11] Patients were interferon naive (not previously treated with interferon), relapsers (patients with a transient biochemical or virological response to previous interferon therapy), or non-responders (patients who did not respond to previous interferon therapy). We excluded patients with hepatitis B, HIV infection, or hepatic decompensation.

Primary outcome measures were virological response (loss of detectable hepatitis C virus RNA) at the end of treatment, at 6 months, and at >6 months after treatment, and liver related morbidity (cirrhosis, hepatocellular carcinoma, and liver transplantation) plus mortality.[11] Secondary outcome measures were biochemical response (normalisation of transaminases) at the end of treatment, 6 months, and >6 months after treatment, improvement of histological activity index and quality of life, and occurrence of adverse events.[11]

Eligible trials (see table on *BMJ*'s website) were identified through electronic searches (up to August 2000) of the controlled trials register of the Cochrane

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A table giving details of the studies in this review is available on the BMJ's website

Hepato-Biliary Group, the Cochrane Library, Embase, and Medline, hand searches of specialist journals and bibliographies, authors of included trials, and pharmaceutical companies.[11] Authors of the present study independently evaluated whether trials fulfilled the inclusion criteria. The quality of the trials' methods was assessed by randomisation and blinding methods.[11–14]

Statistical methods

We analysed data by intention to treat using the last reported observed response (carry forward) and including all patients irrespective of compliance or follow up. Information about missing data was sought from authors of the relevant studies. Binary outcomes were expressed as relative risks and 95% confidence intervals. The number needed to treat was calculated as

$1/(1-\mathrm{RR})\times\mathrm{CER}$

where RR = relative risk and CER = control group event rate. Rare events (morbidity plus mortality) were estimated by Peto odds ratio[15] and quality of life by weighted mean difference. We used a random[16] or fixed effects model[17] on the basis of the presence or absence of heterogeneity ($P<0.1$). The associations between the virological response and intervention regimen, publication status, and methodological quality were assessed by sensitivity analyses. Funnel plot asymmetry was explored by regression analysis.[18]

The effect of patient and trial characteristics on the size of the estimated intervention benefit (virological response) was analysed by random effects meta-regression. A significant association between a characteristic and the benefit of treatment was inferred when a slope was significantly different from zero. A positive slope indicated a positive association and a negative slope indicated a negative association. All analyses were performed in the Cochrane Collaboration's Review Manager software 4.1 and Stata version 6.0 for Windows.

Results

The electronic searches produced 1032 references including 770 duplicates and some references that were clearly irrelevant. The manual searches produced 123 references. From these searches we retrieved 477 relevant references. They comprised 210 reviews and basic science studies, 93 observational studies, 60 randomised trials that did not fulfil the inclusion criteria, 25 trials in which relevant data could not be extracted, 5 ongoing trials, and 84 references describing 48 randomised trials (available on request), of which 21 were published as abstracts.

The trials included 6585 patients who were treated for 6-60 weeks (median 26 weeks) and followed either to the end of treatment (20 trials) or to 12-96 weeks (median 24 weeks) after treatment. Fifteen trials included naive patients, 6 included relapsers, 15 included non-responders, 10 included relapsers and non-responders, and 1 trial included naive patients and relapsers. One trial did not report previous therapy. The mean age of included patients was 43 years (SD 5 years). The median proportion of patients with cirrhosis was 13% (range 0-52%), with genotype 1 infection 59% (0-100%), and of men was 64% (20-100%). The dose of interferon was 3 MU three times a week (22 trials), 4.5 to 5 MU three times a week (n = 8), or 6 MU three times a week (n = 18). The dose of ribavirin was 1000-1200 mg/day (n = 34), 600-800 mg/day (n = 10), or 14-15 mg/kg/day (n = 4). In 10 trials, patients received induction therapy for 2-26 weeks (high dose interferon with or without ribavirin).

Compared with interferon, combination therapy reduced the risk of not having an end of treatment virological response by 28% in naive patients (relative risk 0.72; 95% confidence interval 0.65 to 0.79), 47% in relapsers (0.53; 0.38 to 0.74), and 17% in non-responders (0.83; 0.79 to 0.88) (fig 1). The benefit of combination therapy was sustained 6 months after treatment (fig 2) and >6 months after treatment in naive patients, relapsers, and non-responders (0.75; 0.62 to 0.91). The number needed to treat to achieve one additional sustained virological response lasting 6 months was 6 (4 to 7) in naive patients, 4 (2 to 6) in relapsers, and 7 (6 to 10) in non-responders.

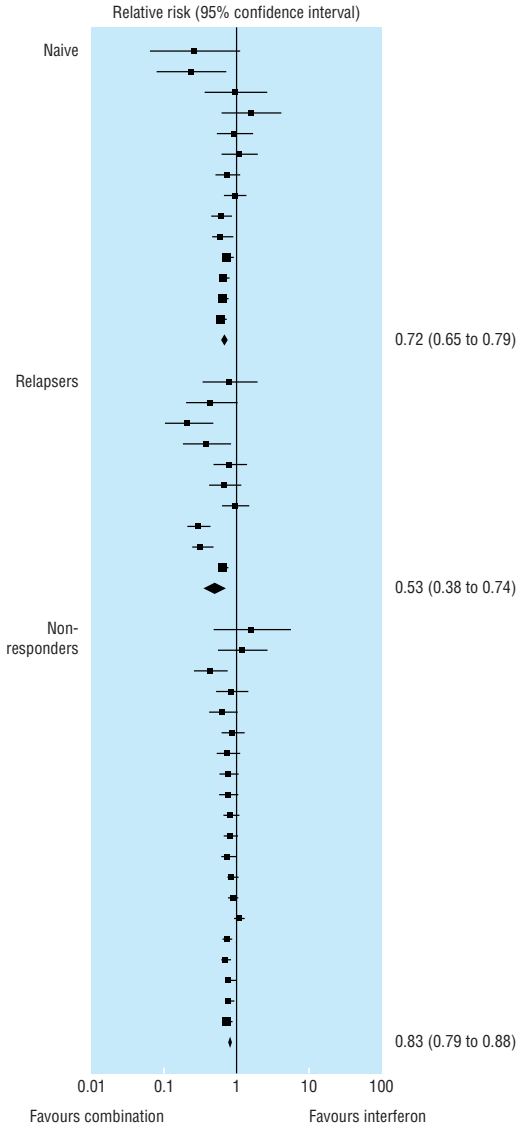

Fig 1 Effect of interferon alfa plus ribavirin combination therapy versus interferon alfa on the risk of not having an end of treatment virological response (random effects model). Trials are sorted according to weight

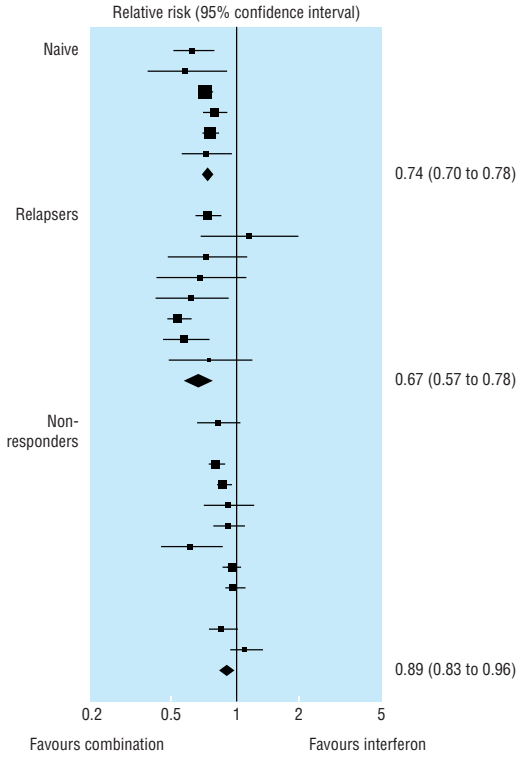

Fig 2 Effect of interferon alfa plus ribavirin combination therapy versus interferon alfa alone on the risk of not having a sustained virological response 6 months after treatment (random effects model). Trials are sorted according to weight

Six patients receiving combination therapy and 12 taking interferon developed cirrhosis confirmed by histology. One patient on interferon developed a hepatocellular carcinoma and none underwent liver transplantation. One patient on interferon committed suicide and one accidental death occurred in each intervention arm. Liver related morbidity plus all cause mortality showed a non-significant trend in favour of combination therapy (Peto odds ratio 0.45; 0.19 to 1.06).

Combination therapy significantly reduced the risk of patients not having a biochemical response at the end of treatment (relative risk 0.63; 0.58 to 0.70), 6 months after treatment (0.76; 0.69 to 0.84), and >6 months after treatment (0.78, 0.64 to 0.94). The reduction in risk was irrespective of previous treatment. Combination therapy significantly reduced the risk of not having an improved histological activity index in naive patients (0.83; 0.74 to 0.93) and in relapsers plus non-responders (0.73; 0.66 to 0.82). One trial assessed quality of life.[19] Combination therapy had a significant benefit on some subscales in two questionnaires applied (data not shown), but the overall results were not conclusive.[19] Combination therapy significantly increased the risk of treatment discontinuation (1.28; 1.07 to 1.52) and dose reductions (2.44, 1.58 to 3.75).

The sensitivity analyses showed no significant differences in the virological response in trials using different intervention regimens (data not shown), abstracts or full paper articles (0.75; 0.69 to 0.81 and 0.75; 0.64 to 0.89, respectively), or in trials with adequate compared to unclear generation of the allocation sequence and allocation concealment (0.74; 0.65 to 0.84 and 0.75; 0.69 to 0.81, respectively). The funnel plot analysis showed no evidence of bias (intercept 1.04, SE 1.06; P = 0.33).

The relation between the benefit of combination therapy assessed by the virological response and trial and patient characteristics were explored by meta-regression. We found a significant positive association between the effect of combination therapy and the proportion of patients with genotype 1 (regression coefficient 0.02, standard error 0.008, P = 0.016) after adjusting for previous treatment, intervention regimen, and patient characteristics. This suggests that patients with genotype 1 benefit more from combination therapy as opposed to interferon than do patients with other genotypes. There was a significant negative association between the benefit of combination therapy and the proportion of patients with cirrhosis (−0.03, 0.013, P = 0.013), suggesting that patients with cirrhosis benefit less from combination therapy. We also found a significant positive association between the virological response and the duration of therapy (0.02, 0.001, P = 0.0001), which suggests that the benefits of combination therapy increase with increasing duration of therapy. There was no significant association between the benefit of combination therapy and age, sex, publication status, or quality of method (generation of the allocation sequence, allocation concealment, and double blinding).

Discussion

Combination therapy had a significant beneficial effect on the sustained virological, biochemical, and histological response of naive patients, relapsers, and non-responders with chronic hepatitis C. Combination therapy also significantly increased the number of adverse events. We found a non-significant trend towards favouring combination therapy as assessed by the number of patients who developed histological signs of cirrhosis, hepatocellular carcinoma, or who died. However, none of the trials followed patients for long enough to assess whether combination therapy has an effect on liver related morbidity or mortality.

The present review includes a few large and several small trials published as abstracts or full articles in many journals. The patients included and the intervention regimens varied considerably. This can be viewed as a weakness and a strength of our review. Limiting our analysis to include only trials using one specified intervention regimen may have provided a more focused answer. However, we chose to assess the benefit of combination therapy under a variety of circumstances to increase the degree of safe generalisation of the results.

The funnel plot analysis showed no evidence of publication bias,[18] but it is still possible that we have not identified all trials. Unpublished trials and trials published as abstracts are especially difficult to identify and are more likely to have a negative result than published trials.[20,21] We identified several abstracts, but no unpublished trials. However, several negative trials would be needed to change the overall results.

The conclusions of the present review are mainly based on surrogate outcomes. The rationale for achieving a sustained virological response is supported by studies indicating that 92% of patients with six months' sustained virological response remain seronegative up

What is already known on this subject

Interferon alfa was the recommended treatment for chronic hepatitis C until the late 1990s

Combination therapy is recommended for previously untreated patients with chronic hepatitis C, but the benefit of treating relapsers and non-responders to previous treatment with interferon remains controversial

The effect of treatment on liver related morbidity and mortality has not been established

What this study adds

Combination therapy is more effective in treating hepatitis C than interferon alfa alone in naive patients, relapsers, and non-responders

Combination therapy significantly reduced the risk of not having a sustained virological or histological response irrespective of previous treatment and may therefore also be considered in relapsers and non-responders to previous treatment

The data indicate a non-significant trend towards a beneficial effect on morbidity plus mortality rates

to six years later[22] and that a sustained virological response to antiviral therapy may be associated with regression of fibrosis.[23 24] However, the question of whether the patients who respond to treatment are the same patients who later develop end stage liver disease is unanswered.[10] Patients who respond to treatment generally have a low baseline risk of complications,[25 26] whereas non-responders have a poorer prognosis.[27] Histological severity, alcohol misuse, and increasing age have been identified as predictors of progression to cirrhosis.[28] In the present review, patients were generally young, without cirrhosis, and had no alcohol abuse. Accordingly, the general baseline risk of patients was low and only few clinical events were reported.

Our results suggest that about 37% of naive patients, 42% of relapsers, and 15% of non-responders obtain sustained virological responses with combination therapy. These data are consistent with previous findings.[29 30] A systematic review of 19 randomised trials and 3765 patients[29] found that 33% of naive patients and 49% of relapsers achieved a sustained virological response on combination therapy. A meta-analysis of 12 trials and 941 patients found that 14% of previous non-responders obtain a sustained virological response on combination therapy.[30] Our results also concur with previous trials that found a beneficial effect of increased duration of therapy.[25 26] The benefit of longer treatment duration may be required in patients with genotype 1 because these patients are less likely to respond to treatment.[29 31]

In conclusion, the present review shows that combination therapy has a beneficial effect on the virological, biochemical, and histological response of patients with chronic hepatitis C, irrespective of previous treatment. However, only 15% of non-responders obtained a sustained virological response and it may be discussed whether combination therapy should be offered to these patients. Other modes of treatment seem promising—for example, pegylated interferon plus ribavirin[32] or interferon plus ribavirin and amantadine[33]—but need further evaluation. Future research should also focus on the effect of treating patients with little or no histological damage and the effect of treatment on liver related morbidity and mortality.

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Contributors: LLK drafted the protocol and paper, performed the literature searches, extracted all data, and performed the statistical analyses. CG validated the data extraction and all contributors took part in the selection of trials for inclusion, the interpretation of data, and writing of the protocol and paper. LLK is the guarantor.

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Unwanted caesarean sections among public and private patients in Brazil: prospective study

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Abstract

Objective To assess and compare the preferences of pregnant women in the public and private sector regarding delivery in Brazil.
Design Face to face structured interviews with women who were interviewed early in pregnancy, about one month before the due date, and about one month post partum.
Setting Four cities in Brazil.
Participants 1612 pregnant women: 1093 public patients and 519 private patients.
Main outcome measures Rates of delivery by caesarean section in public and private institutions; women's preferences for delivery; timing of decision to perform caesarean section.
Results 1136 women completed all three interviews; 476 women were lost to follow up (376 public patients and 100 private patients). Despite large differences in the rates of caesarean section in the two sectors (222/717 (31%) among public patients and 302/419 (72%) among private patients) there were no significant differences in preferences between the two groups. In both antenatal interviews, 70-80% in both sectors said they would prefer to deliver vaginally. In a large proportion of cases (237/502) caesarean delivery was decided on before admission: 48/207 (23%) in women in the public sector and 189/295 (64%) in women in the private sector.
Conclusions The large difference in the rates of caesarean sections in women in the public and private sectors is due to more unwanted caesarean sections among private patients rather than to a difference in preferences for delivery. High or rising rates of caesarean sections do not necessarily reflect demand for surgical delivery.

Introduction

Different rates of caesarean section in public and private patients suggest that non-medical factors, such as economic gain and pressures of private practice, may motivate doctors to perform surgical deliveries. Alternatively, these differences may reflect patients' preferences and result from informed choices about type of delivery.[1–6] In Brazil, choosing between these interpretations is contentious as the rate of caesarean sections among private patients is extremely high and more than twice the rate in the public sector. About one quarter of all deliveries take place in the private sector, and more than 70% of those are by caesarean section.[7 8] Such a rate cannot be attributed to the actions of a fraction of the obstetricians with private practice[9 10] or the prevalence in the population of the usual medical indications for caesarean delivery.[11] The most doctor friendly, but still problematic, explanation is a strong preference for surgical deliveries among the upper and middle class women who are most likely to have private medical insurance.[12]

Brazil is often portrayed as a country where there is an unusually large demand for caesarean sections, especially among more affluent women.[13] The alleged motivations for the choice include fear of vaginal birth, preservation of coital function, relief from the pain of labour, and to obtain a tubal ligation.[14 15] Often the evidence put forward comes from physicians' accounts of women's preferences rather than directly from women themselves.[16–18] In two recent postpartum studies conducted in Brazil among both private and public

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