# Retreatment with pegylated interferon plus ribavirin of chronic hepatitis C non-responders to interferon plus ribavirin: a meta-analysis

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## CRD summary

The review found only modest sustained virological response rates to re-treatment of patients who had failed to respond to pegylated or standard interferon plus ribavirin. The authors recommended restricting re-treatment to 24 weeks, patients who were not overweight, or genotype 2/3 infected patients. The reliability of the authors' conclusions is unclear due to insufficient high-quality evidence.

## Authors' objectives

To evaluate the efficacy and tolerability of re-treatment with pegylated interferon plus ribavirin of patients (with chronic hepatitis C) who failed to respond to pegylated or standard interferon plus ribavirin, with focus on sustained virological response rates and identification of factors influencing them.

## Searching

MEDLINE, EMBASE and the Cochrane Library were searched from inception to April 2009. Search terms were reported. Bibliographies of retrieved reviews, primary studies and meeting abstracts were handsearched.

## Study selection

Randomised controlled trials (RCTs) and prospective cohort studies of patients with chronic hepatitis C, who did not respond to standard or pegylated interferon plus ribavirin, who were re-treated with pegylated interferon plus ribavirin, were eligible for inclusion. Non-response had to be defined as detectable serum hepatitis C virus RNA, three or six months after therapy. The primary outcome was sustained virological response rate. The secondary outcome was tolerability.

Most of the included studies were multi-centre. Where reported among included studies, the majority of patients were male, with a mean age of 47.8 years, and an average BMI of 27.5 kg/$m^2$. The definition of non-response varied: detectable serum hepatitis C virus RNA three or six months after start of therapy, or timing not reported. Few studies provided intervention details, with a large variability in regime: type of pegylated interferon (alpha-2a or alpha-2b) and dose (range 50 to 300μg/week); ribavirin dose (range 800 to 1400mg/day). Treatment length was 48 weeks in all but one study.

The authors did not state how many reviewers performed the selection.

## Assessment of study quality

Methodological quality was assessed using four principle criteria: intention-to-treat analysis; patients enrolled consecutively; non-responsive patients included; and studies did not include patients who relapsed with patients who did not respond. ‘Good’ quality studies were arbitrarily classified as those that met two of the four principle criteria.

Three reviewers independently performed the validity assessment, with disagreements resolved by discussion.

## Data extraction

Sustained virological response rates and 95% confidence intervals (CI) were extracted. The characteristics of patients were specifically extracted in order to identify factors that affected sustained virological response rates.

It appeared that three reviewers performed the data extraction, with disagreements resolved by discussion.

## Methods of synthesis

Univariate logistic regression analysis using a random-effects model, adjusted for sample sizes, was used to pool sustained virological response rates. Between study heterogeneity was determined using $X^2$ tests. Stratum specific sustained virological response rates were calculated for 11 different patient-level and study-level covariates. Publication bias was assessed using the methods of Begg and Berlin (using funnel plots) and Egger et al. Only the full-length papers were included in any analysis but abstracts were used to assess publication bias.

## Results of the review

Fourteen studies were identified (n=3,898 patients), including one RCT (n=942) and 13 prospective cohort studies (n=2,956, range 20 to 1385). Eight studies were classified as 'good' quality. Fifty percent of the studies used an intention-to treat analysis. Six relevant abstracts were also identified.

The pooled sustained virological response rate was 16.3% (95% CI 8.3 to 29.6), with statistically significant heterogeneity.

Similar effect sizes were found after the omission of two outliers from the meta-analysis and the omission of the RCT of patients who did not respond to first treatment. For the seven studies which provided data for sustained virological response rate related to genotype infection, a pooled analysis found a significantly lower sustained virological response rate of 15.6% (95% CI 12.4 to 19.4%) for genotype 1 than for patients infected by genotype non-I infection (sustained virological response 33.9%, 95% CI 25.8 to 43.1) (p=0.0001). Higher pooled sustained virological response rates (more than 20%) were observed for studies with: fewer patients (less than 100); lower mean baseline body mass index (BMI less than 28 kg/m2); fewer cirrhotic patients (less than 20%); and retreatment with pegylated interferon alpha-2a compared with pegylated interferon alpha-2b. No other covariates appeared to significantly influence sustained virological response rate (see paper for details).

Univariate meta-regression of 12 variables found only three variables were significantly associated with an increased rate of sustained virological response: low mean baseline body mass index; low percentage of patents with genotype 1 infection; and treatment with pegylated interferon alpha-2a.

Re-treatment for 48 weeks was associated with high withdrawal (11.65%, 95% CI 10.5 to 12.6), dose reduction (17.6%, 95% CI 16.4 to 18.9), and a high level of serious or life threatening (grade 3 or 4) adverse events (7.1%, 95% CI 6.3 to 8.0).

There was no evidence for publication bias.

## Authors' conclusions

The modest efficacy of re-treatment with pegylated interferon plus ribavirin of all patients who did not originally respond, implied that it should not be used indiscriminately. Restricting re-treatment to patients who were not overweight or to those with genotype 2 or 3 infection, and stopping treatment after 24 weeks, would optimise the potential benefit and be unlikely to miss any positive response.

## CRD commentary

The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched, but it was not clear if any language restrictions were applied, so relevant studies could have been missed. However, there was no evidence of publication bias. Study quality was assessed using suitable criteria, but the quality grade given to included studies was probably too high. Although validity assessment was carried out with efforts to reduce error and bias, it was not reported clearly whether this process applied to other aspects of the review process.

Relevant study details were reported, but some of the data provided in the online appendices did not agree with the text; the online intervention details were not clear. Statistical heterogeneity was assessed and investigated. The statistical method used for the meta-analysis of the RCTs seemed appropriate, but the clinical significance of individual results was not clear. There were limitations related to the quality of the included studies, including study design, populations studied, retreatment regimes and severity of illness at baseline. The authors had reservations about their conclusions related to treatment with different types of interferon and cirrhosis patients.

In view of the limitations in the quality of the included studies, the extent to which the authors' conclusions are reliable is unclear.

## Implications of the review for practice and research

Practice: The authors stated that re-treatment should be restricted to patients who were not overweight or to those with genotype 2 or 3 infection, and that it should be stopped after 24 weeks, to optimise the potential benefit and avoid missing any positive responses. They also recommended that patients could reduce body weight before re-treatment.

Research: The authors identified a need for research using standardised regimes to obtain comparative data on efficacy and safety, particularly regarding ribavirin dose; and large scale multi-centre RCTs to find the benefit of prolonged courses of therapy.

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## Bibliographic details

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