Meta-analysis: combination therapy with interferon-alpha 2a/2b and ribavirin for patients with chronic hepatitis C previously non-responsive to interferon

San Miguel R, Guillen F, Cabases J M, Buti M

Authors' objectives
To assess the efficacy and safety of combination therapy with interferon (IFN)-alpha 2a or 2b plus ribavirin in patients with chronic hepatitis C who have not responded to prior IFN monotherapy.

Searching
MEDLINE, PREMEDLINE, the Cochrane Controlled Trials Register, EMBASE, International PharmaceuticalAbstracts, Derwent Drug File, Pharmaproject, IME, and the MDX Health Digest and MediConf databases were searched for studies carried out between 1993 and November 2001; grey literature was sought in NTIS and SIGLE. The search terms were stated and no language restrictions were applied. In addition, the reference lists of identified studies were checked, and clinicians and pharmaceutical companies were contacted for details of unpublished studies and other relevant information.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of IFN-alpha 2a or 2b (minimum dose: 3 million units, MU, three times per week, t.i.w.) plus ribavirin (minimum dose: 800 mg/day), given for at least 6 months, were eligible for inclusion. The included studies compared IFN plus ribavirin with INF alone for 6 months, or compared different IFN plus ribavirin regimens. The doses used in studies comparing combination therapy with INF alone were 3 MU t.i.w., 6 MU t.i.w. or 5 MU on alternate days for IFN-alpha 2b, or 4.5 MU t.i.w. for IFN-alpha 2a; all of these studies used 1,000 to 1,200 mg/day ribavirin. Studies comparing different regimens compared different treatment durations (6 versus 12 months) and different doses of IFN (3 versus 5 MU).

Participants included in the review
Studies of patients who had not responded to a prior course of IFN treatment (nonresponders) were eligible for inclusion. A nonresponse was defined as an inability to reach a normal serum alanine transaminase level or undetectable serum hepatitis C virus DNA during IFN treatment. Studies of patients with other co-existing disease were not included. The included studies had more male than female patients (range: 52 to 86% male) and, generally, more patients with unfavourable (1 and 4) than favourable (2 and 3) viral genotypes.

Outcomes assessed in the review
The inclusion criteria were not explicitly defined in terms of the outcomes. The primary outcome assessed in the review was the sustained virological response, which was defined as an undetectable serum hepatitis C RNA at least 24 weeks after the end of treatment. The review also assessed the sustained biochemical response (defined as a normal serum alanine transaminase at least 24 weeks after the end of treatment) and safety. Studies reporting the sensitivity limit for measuring hepatitis C virus RNA had similar sensitivity limits and used similar tests to measure the virological response, with a lower limit of between 100 and 1,000 copies/mL.

How were decisions on the relevance of primary studies made?
Two researchers independently conducted the searches.

Assessment of study quality
Validity was assessed using a generic and validated scale that assessed allocation concealment, randomisation, blinding and withdrawals. The authors did not state how the papers were assessed for validity, or how many reviewers performed
the validity assessment.

**Data extraction**

Two researchers independently extracted the data and resolved any disagreements through discussion. Data were extracted on the characteristics of the RCTs, characteristics of the patients, outcomes, safety, financial support and conflicts of interest. Some authors were contacted about missing data.

**Methods of synthesis**

How were the studies combined?

The characteristics of the studies were summarised in the text. The data were analysed on an intention-to-treat basis. A pooled odds ratio (OR) and risk difference, both with 95% confidence intervals (CIs), were estimated using a random-effects (DerSimonian and Laird) model. Pooled ORs were calculated for combination therapy versus IFN alone, for 6 versus 12 months of combination treatment, and for treatment with 3 versus 5 MU of IFN. The number of nonresponders needed-to-treat (NNT) was estimated for combination therapy versus monotherapy. Pooled response rates were calculated for combination treatment, monotherapy, treatment with 3 and 5 MU, and treatment for 6 and 12 months. Pooled rates of flu-like illness and withdrawals were also calculated.

How were differences between studies investigated?

Statistical heterogeneity (P<0.1) was tested using the Q statistic. The influence of each study was assessed by repeating the analysis after omitting each study in turn. The influence of viral genotype (unfavourable or favourable) and study quality (by omitting the RCTs with the lowest quality scores) was also assessed. Trials that included nonresponders and relapers were analysed separately.

**Results of the review**

Ten RCTs (n=1,728) were included.

The quality scores ranged from 0.6 to 0.79 (mean 0.71) on a scale from 0 to 1. Six RCTs described the method of randomisation, but none of the RCTs were blinded to the treatment allocation. Two RCTs did not report the reasons for withdrawal and two did not report the withdrawals separately for nonresponders and relapers.

Virological response.

Combination therapy significantly improved sustained virological response; the pooled OR (5 RCTs, 786 patients) was 5.49 (95% CI: 1.9, 15.9) and the NNT was 10 (95% CI: 7, 17.5). No significant heterogeneity was found (P=0.17).

Sustained virological response was also improved with combination therapy for 12 months, compared with 6 months’ treatment, and with combination therapy using 5 MU versus 3 MU. The pooled ORs were 1.54 (3 RCTs, 474 patients; 95% CI: 0.94, 2.51) and 1.39 ((3 RCTs, 427 patients; 95% CI: 0.78, 2.49), respectively, and no significant heterogeneity was found (P=0.99 and P=0.61, respectively). For all 10 studies combined, combination therapy (any regimen or duration) significantly improved the response rate; the risk difference was 16.2% (95% CI: 14.3, 18.3).

Biochemical response (5 RCTs).

Combination therapy improved sustained biochemical response in comparison with IFN alone, but data from only 2 RCTs were pooled; the pooled OR was 2.1 (2 RCTs, 403 patients; 95% CI: 0.4, 11).

Safety.

Only 2 RCTs reported all the side-effects. Combination treatment and IFN alone had similar rates of flu-like symptoms: 63% (95% CI: 60, 66) and 60% (95% CI: 54, 66), respectively. It was not possible to assess the association between ribavirin and haemolytic anaemia due to differences in the methods of reporting.

Withdrawals. Adequate data on withdrawals were only presented in 7 RCTs. The rates of withdrawal due to adverse effects were 8.8% (95% CI: 6.5, 11.6) with combination therapy and 4% (95% CI: 2.1, 6.7) with IFN alone. The rates
of withdrawal due to any cause were 14% (95% CI: 12.1, 16.1) and 8.3% (95% CI: 5.5, 11.8), respectively, for combination therapy and IFN alone.

**Authors’ conclusions**
In patients with hepatitis C who fail to respond to IFN, combination therapy increased the response rates to re-treatment, especially if the treatment was given for 48 weeks, compared with IFN alone. However, the sustained response rates, even with longer treatment, did not exceed 20%.

**CRD commentary**
This was a well-conducted and clearly presented review. The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched for published and unpublished studies, no language restrictions were applied, and the search terms were stated. Two reviewers independently conducted the searches and extracted the data, which reduces the potential for bias and errors. Validity was assessed using validated criteria and relevant information on the included studies was tabulated. Statistical heterogeneity was assessed and the data were appropriately pooled in a meta-analysis. A sensitivity analysis was used to explore the influence of single studies, patient characteristics and study quality on the results. The evidence presented appears to support the authors’ conclusions.

**Implications of the review for practice and research**
Practice: The authors stated that nonresponders to an initial course of IFN may have a greater response to combination therapy than to re-treatment with INF alone.

Research: The authors stated that there is a need to standardise the design and reporting of trials of treatment for patients with hepatitis C. In addition, factors that influence response (drug dose, viral genotype) should be explored.

**Bibliographic details**

**PubMedID**
12197840

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Antiviral Agents /adverse effects /therapeutic use; Drug Therapy, Combination; Female; Hepatitis C, Chronic /drug therapy; Humans; Interferon-alpha /adverse effects /therapeutic use; Male; Middle Aged; Randomized Controlled Trials as Topic; Recombinant Proteins; Ribavirin /adverse effects /therapeutic use

**AccessionNumber**
12002002061

**Date bibliographic record published**
31/05/2004

**Date abstract record published**
31/05/2004

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.