Treatment of chronic hepatitis C in haemophilic patients with interferon and ribavirin: a meta-analysis

CRD summary
This review evaluated the efficacy of interferon (IFN) and ribavirin in the treatment of chronic hepatitis C in haemophilic patients and concluded that the pattern of response in HCV-infected haemophilics is similar to that in the general HCV-infected population. The reliability of the conclusions is limited by the weak evidence base and incomplete reporting of the review process.

Authors' objectives
To evaluate the efficacy of a combination of interferon (IFN) and ribavirin (RBV) in the treatment of chronic hepatitis C in haemophilic patients.

Searching
MEDLINE, EMBASE, SCOPUS, Cochrane Library and bibliographies of relevant studies and reviews were searched. Search dates were not reported, but search terms were reported. Unpublished studies were sought from relevant conference abstract books.

Study selection
Controlled, uncontrolled, randomised or non-randomised studies of patients with hereditary bleeding disorders and chronic hepatitis C virus (HCV) treated with IFN plus RBV or pegylated-IFN (Peg-IFN) plus RBV were eligible for inclusion. Only combination therapies planned for ≥6 months were considered. The outcomes of interest were sustained viral response (SVR) and predictors of response to treatment. Further details of the definitions of eligible outcomes and predictors of treatment were given in the report.

The treatments evaluated in the included studies were IFN plus RBV and Peg-IFN plus RBV. The doses varied between the studies (full details reported in the paper for all except one study). The duration of treatments ranged from six to 12 months. All the included studies reported SVR (defined as undetectable HCV-RNA six months after the end of treatment) as a primary outcome. Details of the disease states were not reported fully in the tables.

The authors did not state how the papers were selected for review nor how many reviewers performed the selection.

Assessment of study quality
Study validity was assessed using two scales: the Newcastle-Ottawa scale assessing for selection bias, comparability of cohorts and outcomes was used for cohort studies; the Jadad scale (giving a score between 0 and 5) assessing randomisation, blinding and withdrawals was used for randomised controlled trials (RCTs).

Two reviewers independently assessed study quality, with disagreements referred to a third reviewer.

Data extraction
The authors did not state how the data were extracted for the review nor how many reviewers performed the data abstraction.

Methods of synthesis
A pooled odds ratio (OR) and corresponding 95% confidence interval (CI) was calculated using the DerSimonian and Laird method where trials reported outcome data in separate arms. A non-comparative effect size (success rate) was calculated using meta-regression where trials did not report the outcome in separate study arms. Study results were weighted using the inverse variance method. The influence of predictors on success rate in HCV eradication was assessed using meta-regression. Statistical heterogeneity was assessed using the Cochran’s Q test and I² statistic.
Publication bias was assessed using a funnel plot and a range of statistical tests.

Results of the review
Eighteen studies were included (n=824): three RCTs (n=240), 14 prospective cohorts (n=560) and one retrospective study (n=24). A majority of studies had small sample sizes (n<50). A majority of the cohort studies were rated as satisfactory and homogeneous using the Newcastle-Ottawa scale. The mean Jadad score was 3.

Overall
Genotype 1 was associated with a statistically significant lower SVR compared with non-1 genotypes in HIV-negative patients (OR 0.15, 95% CI: 0.09, 0.25). There was a statistically significant lower SVR in HCV-HIV co-infected patients compared to patients with HCV infection only (OR 0.25, 95% CI: 0.08, 0.81). There was a statistically significant higher rate of SVR in HIV-negative naïve haemophiliacs treated with Peg-IFN (Effect Size (ES) 0.61, 95% CI: 0.54, 0.68). However, a statistically significant lower SVR was reported in HIV-positive naïve haemophiliacs treated with Peg-IFN (ES 0.29, 95% CI: 0.13, 0.51). HIV-negative naïve haemophiliacs treated with Peg-IFN had a higher rate of SVR (61%).

RCTs
Results on rates of response to RCTs were limited to HIV-negative patients. In one RCT, the rate of SVR was 28.5 per cent in patients receiving non-Peg-IFN with ribavirin. In another, the rates of SVR were 21.9 per cent for genotype 1 and 80.0 per cent for non-1 genotypes. A third RCT reported SVR rates of 39.2 per cent for genotype 1 and 86.6 per cent for non-1 genotypes.

There was no evidence of publication bias.

Authors’ conclusions
The pattern of response to IFN or Peg-IFN plus ribavirin in chronically HCV-infected haemophiliacs is similar to that in the general HCV-infected population.

CRD commentary
The review inclusion criteria were clear with respect to study designs, participants, treatments and outcomes. Relevant databases were searched and reference lists were reviewed to locate additional information. Efforts were made to locate unpublished material. However, it was unclear if language restrictions were applied, hence language bias cannot be ruled out. Publication bias was assessed adequately. It is not clear if study selection and data extraction were done in duplicate, hence reviewer error and bias cannot be ruled out. Methodological quality was assessed independently by two reviewers using appropriate criteria and the results reported. Statistical heterogeneity was assessed and the results reported. The statistical methods used in the meta-analysis were justified, although details were not reported fully. The use of meta-regression to assess the influence of predictors on outcome was not appropriate given the limited number of data sets per variable investigated. The authors’ conclusions were supported by the data presented, although lack of clarity in reporting some review process made it difficult to rule out possible errors or biases. Overall, given the limited evidence from high quality studies (most trials were cohort studies), the authors' conclusions should be treated with caution.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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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.