Meta-analysis: ribavirin-induced haemolytic anaemia in patients with chronic hepatitis C

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Authors' objectives
To use meta-analysis to study the risk of anaemia related to ribavirin therapy for chronic hepatitis C.

Searching
MEDLINE was searched for studies published before January 2001; the search terms were reported. The reference lists of identified reports and three recently published reviews on treatment for chronic hepatitis C were also reviewed. Only studies reported in the English language were eligible for inclusion.

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 that compared ribavirin plus interferon (IFN) versus IFN alone, placebo or no intervention, or studies comparing ribavirin monotherapy versus placebo or no intervention, were eligible for inclusion. Trials were included regardless of the dose, length of therapy, or regimen of ribavirin and IFN. The actual dosages of ribavirin in the included trials ranged from 600 to 1,200 mg/day. IFN was given at a dose of 3 to 6 MU three times a week. The therapy was given for either 24 or 48 weeks.

Participants included in the review
Studies of adult patients with chronic hepatitis C were eligible for inclusion. Studies including patients co-infected with hepatitis B virus or human immunodeficiency virus, patients who had undergone organ transplantation, or patients who had received any immunosuppressive therapy were excluded. The studies included patients who had never received any antiviral therapy (naive patients), had relapsed after IFN therapy, or who had shown resistance to prior IFN therapy. The mean age of the patients ranged from 33 to 50 years and the proportion of male patients ranged from 40 to 100%.

Outcomes assessed in the review
The authors stated that the outcome of interest was the proportion of patients who met one of the following three criteria: withdrawal from the study due to anaemia; reduction of ribavirin dosage due to a decrease in haemoglobin; and decrease in haemoglobin level to less than 10 g/dL. Studies that did not report these safety outcome data were excluded from the review.

How were decisions on the relevance of primary studies made?
Two physicians independently evaluated each study for inclusion in the review and resolved any disagreements through discussion. The authors did not state whether the physicians were blinded to the study author or results.

Assessment of study quality
The studies were evaluated for quality based on the following criteria: patient selection, inclusion and exclusion criteria, allocation sequence, concealment of allocation, blinding, treatment strategy and follow-up. For each question the studies were assigned a score of 0 (inappropriate), 1 (fair) or 2 (appropriate); the maximum possible score was 14. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on the study, participant and intervention characteristics, and efficacy outcomes.
Methods of synthesis
How were the studies combined?
A random-effects model was used to estimate the summary risk difference and 95% confidence interval (CI) of the combined haematological safety outcomes between the treatment and control groups.

How were differences between studies investigated?
Subgroup analyses were conducted based on whether participants were naive versus those who had relapsed or not responded to prior therapy; whether the treatment duration was 24 weeks versus 48 weeks; and whether the ribavirin dose was 800 mg/day or less versus 1,000 mg/day or more. A subgroup analysis was also conducted for the subset of reports from North American and European countries.

Results of the review
Seventeen RCTs with a total of 3,520 patients were included in the review. The search identified 61 potentially relevant English language RCTs: copies of 21 reports were unavailable; 17 of the 40 available reports were eligible for inclusion.

There was significant heterogeneity among the studies in terms of the proportion of patients who developed the combined haematological safety outcome of interest (P<0.001).

Patients taking ribavirin were at significantly higher risk of developing anaemia than those not taking ribavirin. The overall risk difference (ribavirin versus no ribavirin) ranged from 0 to 0.30, with an overall effect estimate of 0.09 (95% CI: 0.04, 0.13). However, patients treated with a ribavirin dose of 800 mg/day or less did not show a significant risk of developing anaemia (risk difference 0.01, 95% CI: -0.04, 0.06), whereas patients treated with a dose of 1,000 mg/day or more were at significantly higher risk of developing anaemia (risk difference 0.09, 95% CI: 0.04, 0.14). There was a statistically significantly higher risk difference reported by the two Asian studies (0.22 and 0.29) compared with that reported by the 15 non-Asian studies (pooled risk difference 0.07, 95% CI: 0.03, 0.12).

Recent studies showed a trend for a decreased incidence of anaemia during ribavirin treatment when compared with older studies. There was no significant difference in risk reported between the following studies: those with fewer than 100 patients versus those with more than 100 patients; naive patients versus nonresponders or relapsers; patients treated for 24 weeks versus those treated for 48 weeks; patients who received ribavirin-IFN combination therapy versus ribavirin alone.

The quality scores of the studies ranged from 4 to 12.

Authors' conclusions
Patients with chronic hepatitis C who were treated with 1 g or more of ribavirin per day had a higher risk of developing anaemia. However, there was a significant difference in risk between the studies reviewed, with the reported risks being higher among Asian studies, possibly due to differences in study entrance criteria, dosage titration strategy or ethnic vulnerability.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes of interest. The search strategy was restricted to searching one computerised database with additional handsearching of reference lists. No attempts were made to search for unpublished research and only reports in English were eligible for inclusion in the review, thus allowing the introduction of publication and language bias; publication bias was not assessed. One third of the studies identified by the search were unavailable, thus increasing the chance that other relevant studies were excluded from the review. Two reviewers independently assessed the studies for inclusion. However, no details of the quality assessment and data extraction processes were given; the possibility of reviewer bias or error cannot, therefore, be assessed.

Adequate details of the included studies, including the quality score, were tabulated. The statistical methods used to pool the studies appear to have been appropriate. There was significant heterogeneity among the studies in terms of the
proportion of patients who developed anaemia, which was investigated in subgroup analyses and discussed in the text. However, in view of the probability of other relevant studies being missed, coupled with the significant heterogeneity in the effect size among the included studies, the overall risk difference reported may not be reliable. The finding of a higher risk of anaemia in patients treated with 1 g or more of ribavirin per day merits further investigation.

**Implications of the review for practice and research**

Practice: The authors stated that close monitoring of haemoglobin levels and judicious adjustment of the ribavirin dosage will markedly reduce the number of patients experiencing clinically significant anaemia during ribavirin therapy.

Research: The authors did not state any implications for further research.

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