Pegylated-interferon and ribavirin in liver transplant candidates and recipients with HCV cirrhosis: systematic review and meta-analysis of prospective controlled studies


CRD summary
The authors concluded that full doses of pegylated-interferon plus ribavirin were effective in patients with hepatitis C virus cirrhosis who were liver transplant candidates or recipients, but the sustained virological response rate was low. Differences between studies, incomplete information about individual studies and limited quality assessment suggest that the findings should be interpreted with caution.

Authors' objectives
To evaluate the efficacy, tolerability and safety of pegylated-interferon plus ribavirin (Peg/R) in patients with hepatitis C virus (HCV) cirrhosis who were liver transplant candidates or recipients.

Searching
MEDLINE and The Cochrane Library were searched from 1999 to January 2008 using reported search terms. English and non-English publications were eligible. Reference lists of reviews and original studies were screened. Abstracts from specified international meetings on liver disease, gastroenterology and transplants were handsearched. Studies could be published as abstracts or full papers.

Study selection
Prospective randomised controlled trials (RCTs) or controlled trials that evaluated the effect of pegylated interferon alpha-2a or alpha-2b plus ribavirin on sustained virological response (SVR) in patients with HCV cirrhosis who were liver transplant candidates or recipients were eligible for inclusion. Treatment duration had to be at least 24 weeks, hepatitis C had to be detected by a sensitive method and pegylated interferon had to be used throughout the treatment period. Patients who also had HIV (human immunodeficiency virus) or hepatitis B were excluded. The review defined sustained virological response as undetectable HCV-RNA in blood using polymerase chain reaction methods six months after the end of treatment. The review also assessed histological response in post-transplant patients six to 12 months after the end of treatment and safety (treatment discontinuation, mortality, acute rejection, chronic rejection and de novo autoimmune complications).

The review compared Peg/R that contained 800mg to 12,000mg ribavirin (group A treatment) versus Peg/R that contained low-dose ribavirin (generally 600mg to 800mg), Peg alone or no treatment (group B treatment). Doses of Peg varied. Some studies also administered growth hormone. Peg/R was evaluated in liver transplant candidates and as a treatment for recurrent HCV disease post transplant. Where reported, some patients were interferon naïve and others had received previous treatment.

The authors reached agreement about studies to be included.

Assessment of study quality
Three reviewers independently assessed and scored the quality of RCTs published as full papers using the Jadad scale (randomisation, blinding and reporting of withdrawals). The maximum possible score was 5 points.

Data extraction
For each study, where possible, numbers or percentages of patients with outcomes of interest were presented. Two reviewers independently extracted data on an intention-to-treat basis onto a standardised form.

Methods of synthesis
Separated analyses were conducted for liver transplant candidates and for treatment of recurrent HCV disease post transplant. Average event rates were calculated for group A and B treatment arms. Where the authors considered it appropriate, pooled risk differences (RD) were calculated using a random-effects model. Heterogeneity was assessed.
using the Q and the I² statistics. Subgroup analyses were used to examine the influence of the following on the effects of Peg/R for treatment of recurrent HCV disease post transplant: randomisation; use of growth factor; and control (no treatment or active control). Differences between studies were discussed with respect to genotype. Publication bias was assessed using a funnel plot.

**Results of the review**

Nine controlled trials were included (n=619): six RCTs (n= 394) and three non randomised studies (n=225).

**Liver transplant candidates (two RCTs and one non randomised study, n=335):** The RCTs scored 5 and 3 out of 5 for quality. Mean sustained virological response rates were 30% (range 19.6% to 50%) for group A treatment arms (Peg/800 to 1,200mg R, n=181) compared with 16% (range 0% to 38%) for group B treatment arms (Peg/low-dose R, no treatment or Peg monotherapy, n=174). One RCT reported no significant difference in discontinuation rates between Peg/R and Peg alone; the statistical significance of treatment differences in other studies was not reported. Two studies reported mortality, but the statistical significance of treatment differences were not reported.

**Treatment for recurrent HCV disease post transplant (four RCTs and two non-randomised studies, n=264):** The two RCTs published as full reports scored 3 and 4 out of 5 for quality. Mean sustained virological response were 41% (range 30% to 78%) for group A treatment arms (Peg/800 to 1,200mg R, n=140) compared with 9% (range 0% to 50%) for group B treatment arms (Peg/low-dose R, no treatment or Peg monotherapy, n=124).

Peg/800 to 1,200 mg R was associated with a statistically significant increase in sustained virological response compared to control treatments (absolute risk difference 0.31, 95% CI 0.18 to 0.44, p<0.001). Significant heterogeneity was found (p=0.058, I²=59%).

There was no significant difference between Peg/800 to 1,200 mg R versus no treatment or other regimen treatments in histological response (significant heterogeneity was found, I²=94%), discontinuation of treatment, acute or chronic rejection or mortality.

The funnel plot showed no evidence of publication bias for recurrent HCV patients (p=0.08 for test of asymmetry).

**Authors' conclusions**

Full doses of pegylated-interferon plus ribavirin were effective in patients with hepatitis C virus cirrhosis who were liver transplant candidates or recipients, but the sustained virological response rate was low.

**CRD commentary**

The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched and attempts were made to minimise publication and language biases. Appropriate methods were used to minimise reviewer error and bias during the review process. Only RCTs published as full papers were assessed for validity, therefore, the validity of the evidence from studies of other designs was unknown. Average event rates were calculated despite wide variation across treatment arms; this method of combining studies took no account of differences within studies. In view of the diversity among studies and in the case of histological response different directions of treatment effect, meta-analysis may not have been appropriate. However, the influence of study design and control group was explored in subgroup analyses. The lack of quality assessment combined with limited reporting of patient demographics and primary study details made it difficult to judge the reliability or generalisability of the reported results.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that multicentre RCTs were required to evaluate the long-term effects of Peg/R and identify methods to reach and maximise the tolerated doses. The efficacy and tolerability of newer agents for HCV also needed to be evaluated.

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