Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin

Berenguer M

CRD summary
This review assessed the effectiveness of pegylated interferon alfa plus ribavirin for management of recurrent hepatitis C. The author concluded that antiviral therapy yielded lower efficacy in liver transplant recipients than in the non-transplant population and that maintenance therapy conferred potential benefits. A number of shortcomings in the review process mean that the author's conclusions cannot be considered reliable.

Authors' objectives
To assess the effectiveness of pegylated interferon (PEG-IFN) alfa plus ribavirin for the management of recurrent hepatitis C (HCV) following liver transplantation.

Searching
MEDLINE was searched for English-language studies from January 2002 to January 2007; search terms were reported. Reference lists of included articles were handsearched to identify additional articles.

Study selection
Eligible studies assessed PEG-IFN alfa-2a or PEG-IFN alfa-2b, plus ribavirin for the management of recurrent acute or chronic HCV after liver transplantation; HCV diagnosis was by either detectable HCV RNA (ribonucleic acid) or histological proof through graft biopsy. Studies were required to state the number of liver transplant recipients infected with HCV who received therapy with PEG-IFN alfa plus ribavirin. Most included studies were retrospective in nature. Dose (where stated) for PEG-IFN alfa-2b ranged between 0.5µg/kg and 1.5µg/kg per week. Dose for PEG-IFN alfa-2a ranged between 90µg and 180µg per week. Dose for ribavirin was between 200mg/day and 1,200mg/day. Excluded studies were: those where transplant recipients did not receive histological assessment and were treated pre-emptively; and those in which patients received standard interferon, did not receive ribavirin or where patients were co-infected with HCV and HIV (human immunodeficiency virus). Articles published in Transplantation Proceedings were excluded. Median age of patients in the included studies was 53.8 years (range 48.5 to 61.4 years); 71% were male. Mean time from liver transplantation to therapy was 24.3 months. Some 86% of patients were infected with HCV genotype 1 and 74% had not previously received PEG-IFN alfa plus ribavirin.

The authors stated neither how the papers were selected for review nor how many reviewers performed the selection.

Assessment of study quality
The authors did not assess validity in a formal manner.

Data extraction
Data on sustained virological response and further outcomes (biochemical response, early virologic response, end-of-treatment virologic response, histologic response, sustained virological response by genotype, tolerability) were extracted as percentages.

The authors stated neither how data were extracted for the review nor how many reviewers performed the selection.

Methods of synthesis
A narrative synthesis was provided, supported by tables. Differences between studies were discussed in the text. It appeared that the authors estimated rates by summing responders and dividing by the total number of patients.

Results of the review
A total of 19 studies (eight prospective and uncontrolled, three prospective and controlled and eight retrospective and
uncontrolled) were included in the review (n=611, range 12 to 61).

In patients who received PEG-IFN alfa plus ribavirin, the mean rate of sustained virological response after transplantation was 30.2% (range 0% to 50%; 19 studies), end-of-treatment virologic response was 42.2% (range 17% to 68%; 18 studies) and biochemical response was 54.8% (range 23% to 75%; 15 studies). The mean sustained virological response rate for genotype 1 patients was 28.7% (range 12.5% to 40%; 10 studies). Dose reduction occurred in 73% and premature discontinuation of treatment in 27.6% of treated patients. The incidence of rejection was 6.4% (range 0% to 25%). Variables most frequently associated with sustained virological response were early virologic response, infection with HCV genotype 2, adherence to therapy and baseline viraemia.

**Authors’ conclusions**
Antiviral therapy yielded lower efficacy in liver transplant recipients than in the non-transplant population; maintenance therapy had a potential benefit in this setting.

**CRD commentary**
The review question and inclusion criteria were clear. The literature search was limited to one database and restricted to English-language publications. There was no specific search for unpublished studies. Therefore, publication and language biases could have been present and studies may have been missed. The methods used for study selection and data extraction were not reported, so it was unclear whether methods were used to minimise error and bias. The authors suggested that they had assessed study quality, but there was no formal assessment of quality of the included studies. Included studies were small and nearly all contained fewer than 60 participants. The methods for pooling the studies were inappropriate in the absence of weighting. In light of the shortcomings highlighted for the review process, lack of assessment of study quality, a paucity of experimental studies and the small sample sizes, the authors’ conclusions cannot be considered reliable.

**Implications of the review for practice and research**
**Practice:** The author did not state any implications for practice.

**Research:** The author stated that there was a need for well-designed large prospective studies to assess combination therapy with pegylated interferon alfa plus ribavirin in transplant recipients and non-transplant patients.

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