Interferon treatment in hemodialysis patients with chronic hepatitis C virus infection: a systematic review of the literature and meta-analysis of treatment efficacy and harms


CRD summary
This review concluded that interferon and pegylated-interferon treatment of haemodialysis patients with chronic hepatitis C virus infection improved sustained virological response, but adverse event rates were high. The clinical variation and methodological weaknesses in the included studies, together with limitations in the review process and analysis, mean that the extent to which the authors' conclusions are reliable is unclear.

Authors' objectives
To assess the efficacy and harms of interferon and pegylated interferon treatment of haemodialysis patients with chronic hepatitis C virus infection.

Searching
MEDLINE (1966 to September 2007) was searched, with no language restrictions. Search terms were reported. Reference lists of retrieved papers were reviewed. Major nephrology and hepatology proceedings were searched for additional studies.

Study selection
Prospective studies that examined interferon-based treatment in interferon-naive patients with chronic hepatitis C virus infections (documented by hepatitis C virus RNA testing) were eligible for inclusion. To be included, studies had to report hepatitis C virus RNA results for at least five months after treatment using quantitative assay. Studies of acute infection, studies that reported change in transaminase levels or liver histology score only, case reports, letters to editors, editorials, and small case series (less than 10 patients) were excluded.

The included studies assessed interferon, pegylated interferon, and pegylated interferon plus ribavirin. Interferon was administered three times every week in all the studies, with the dose ranging from 1 million units (MU) to 6 MU. Pegylated interferon was administered once weekly for six to 12 months, with varying doses. Definition of adverse events varied.

The mean age of included patients was 44 years (range 37 to 54 years); most were male (61%). Treatment duration ranged from four to 12 months (where reported). The mean duration of haemodialysis therapy was 77 months (24 to 192 months); the mean duration of hepatitis C virus was 65 months (range 20 to 94 months). Median pre-treatment hepatitis C virus level was 180,952 IU/mL, and mean RNA level was 514,700 IU/mL. Control treatments in the RCTs were mostly placebo or no treatment. In the 78% of studies that reported hepatitis C virus genotype, the prevalence was 72% for genotype 1, 3% for genotype 2, 13% for genotype 3, and 13% for genotype 4.

The authors did not state how many reviewers selected the studies.

Assessment of study quality
The authors did not state if quality of the included studies was assessed.

Data extraction
One reviewer extracted data for calculating risk difference, treatment event rates and sustained virological response and 95% confidence intervals (CIs). Quantitative hepatitis C virus RNA results were standardised to international units per millilitre using standard conversion formulae. For the studies that reported hepatitis C virus RNA results beyond six months after treatment, sustained virological response at six months was imputed. Individual patient data (IPD) were extracted when summary data were not available. Data on adverse events (including stopping treatment and losses to follow-up) were extracted.
When data were unclear or required assumptions, the other reviewers were consulted to achieve consensus.

**Methods of synthesis**
The efficacy of interferon-based treatment of hepatitis C virus-infected haemodialysis patients was reported as sustained virological response with 95% confidence intervals in a meta-analysis, using the random-effects model of DerSimonian and Laird methods. When there were no control groups, the overall estimate of sustained virological response, adverse events, and treatment discontinuation rates were determined from random-effects model on an intention-to-treat (ITT) analysis. Heterogeneity between trials was assessed by the Cochran $\chi^2$ statistic.

Where necessary, subgroup analyses were conducted to explore the relationship between selected factors.

**Results of the review**
Twenty-five studies met the inclusion criteria (n=594 patients, range 10 to 70). Only six studies were RCTs; few details were provided on the design of the remaining studies, although it appeared that they were cohort studies.

**Sustained virological response**: The overall sustained virological response rate for interferon (alone or with ribavirin) was 41% (95% CI 33 to 49), but $\chi^2$ test-statistic showed a highly statistically significant heterogeneity (p<0.0001). The sustained virological response rate for pegylated interferon was 37% (95% CI 9 to 77). In three RCTs, the risk difference was 37% (95% CI 18 to 55) in favour of interferon. Spontaneous clearance of the infection was achieved in 1% of 84 untreated patients.

**Adverse events**: Frequently reported adverse events associated with interferon were influenza-like illness (41%), anaemia (23%), symptomatic rejection of non-functioning kidney allograft (14%), depression (10%), leukopenia (9%), confusion (7%), diarrhoea (7%), thrombocytopenia (5%), and seizures (4%). The median adverse events rate was 28%. For patients treated with for interferon, the overall weighted rate was 34% (95% CI 23 to 46; 17 studies). For patients treated with pegylated interferon, the rate of adverse events was 20 to 100%, with an overall rate of 50% (95% CI 13 to 86; three studies). Adverse events caused a treatment discontinuation rate of 26% (95% CI 20 to 34) for interferon compared with 28% (95% CI 12 to 53) for pegylated interferon, with higher doses leading to increased discontinuation rates.

These findings did not change significantly in any of the subgroup analyses.

**Authors’ conclusions**
Interferon-based treatment of hepatitis C virus-infected haemodialysis patients showed significant efficacy on sustained virological responses, but a significant increase in the rate of adverse events.

**CRD commentary**
This review addressed a well-defined question in terms of participants, interventions, outcomes, and study design. The search included some relevant data sources; the authors reported searching conference proceedings for additional studies or abstracts. Although more than one reviewer extracted data, but it was unclear how many reviewers selected studies, so the possibility of errors and bias could not be ruled out.

No assessment of study quality was reported, which made it difficult to evaluate the strength of the evidence. The characteristics of the individual trials were presented; most studies were small and without control groups, so may have been prone to substantial biases. The pooling of heterogeneous data (including RCT data with cohort study data) was questionable. Also, adverse events results for RCT comparator groups were only reported in one trial. Potential sources of heterogeneity were explored and reported. Subgroup analyses were conducted.

The clinical variation and methodological weaknesses in the included studies, together with limitations in the review process and analysis, mean that the extent to which the authors’ conclusions are reliable is unclear.

One author disclosed financial links with the pharmaceutical companies Idenix, Novartis and Schering-Plough (all manufacturers of interferon drugs).
Implications of the review for practice and research

**Practice:** The authors stated that clinicians should consider treating stable hepatitis C virus-infected patients undergoing haemodialysis with interferon in doses of at least 3 MU for a minimum of six months, but with careful monitoring for potential adverse events.

**Research:** The authors stated that further research is warranted to evaluate whether pegylated interferon and ribavirin therapy in haemodialysis patients would lead to greater sustained virological response rates than non ribavirin-based treatment; also additional research is needed to investigate the relationship between interferon pharmacokinetics and sustained virological response.

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