Interferon monotherapy for dialysis patients with chronic hepatitis C: an analysis of the
literature on efficacy and safety

Russo M W, Goldswieg C D, Jacobson I M, Brown R S

CRD summary
This review found that patients undergoing dialysis have a greater sustained viral response to interferon monotherapy
than patients with normal renal function, but the authors recommended that patients should be monitored closely for
asthenia, leukopenia and neurotoxicity. The review and the included studies had a number of limitations and the
evidence presented was insufficient to support the authors’ conclusions.

Authors’ objectives
To assess the efficacy and safety of interferon (IFN) monotherapy for chronic hepatitis C virus (HCV) in dialysis
patients.

Searching
MEDLINE and EMBASE were searched from 1986 to 2001 for studies published in the English language; the
keywords were listed. In addition, the reference lists in identified studies were checked.

Study selection
Study designs of evaluations included in the review
The inclusion criteria were not specified in terms of the study design. Randomised controlled trials (RCTs) and
prospective studies were included in the review.

Specific interventions included in the review
Studies of IFN monotherapy were eligible for inclusion if they reported the dose and duration of treatment. Most of the
included studies used 3 million units (MU) of IFN, three times a week; other studies used 5 or 6 MU. The duration of
treatment in studies using an IFN dose of 3 MU ranged from 6 to 12 months.

Participants included in the review
Studies of patients on haemodialysis or peritoneal dialysis were eligible for inclusion. Only studies of patients with
chronic HCV who had not previously been treated with IFN were included. Studies of patients with renal insufficiency
who were not on haemodialysis or peritoneal dialysis, and studies of patients who had received transplants, were
excluded. Most (57%) of the patients in the studies using an IFN dose of 3 MU were genotype 1; the studies also
included a small number of patients with genotypes 2, 3, 4 and 5. Where reported, the mean duration of dialysis in the 3
MU studies ranged from 45 months to 9.4 years.

Outcomes assessed in the review
Studies that assessed sustained viral response (SVR) were eligible for inclusion. The review defined SVR as a negative
HCV RNA by polymerase chain reaction (PCR) at least 6 months after the end of treatment. Studies that did not use
PCR to assess viral response were excluded, as were those that only assessed biochemical response rates.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion in the analysis.

Assessment of study quality
Validity was assessed and scored using the following criteria: randomisation; details of losses to follow-up reported for
all patients; stratification of virological response by genotype; reasons given for all patients who discontinued treatment;
and description of the PCR assay. All criteria were scored equally. The maximum possible score was 100 points The
authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The reviewers extracted data on an intention-to-treat basis.

The proportions of patients with SVR and adverse effects were calculated. The percentage of patients with SVR in the individual studies was tabulated.

**Methods of synthesis**

How were the studies combined?
The results from studies that used 3 MU IFN were pooled using a random-effects model. The results from studies that used higher doses were combined in a narrative.

How were differences between studies investigated?
The statistical heterogeneity of studies using 3 MU IFN was assessed using the Breslow-Day test. For studies of 3 MU IFN, the results for patients with genotype 1 were analysed separately. The pooled SVR was also calculated after omitting one outlying study and for studies with a treatment duration of 6 months (after excluding those with a 12-month treatment duration). It was unclear which studies were involved in these analyses.

**Results of the review**

Eleven studies (213 patients) were included.

The validity scores of studies using 3 MU IFN ranged from 60 to 100. All but one study reported the PCR assay used. Only one study reported the lower limit of detection of the assay.

**IFN dose 3 MU (8 studies, 152 patients).**

The SVR in individual studies ranged from 19 to 68%, while the pooled SVR was 33% (95% confidence interval, CI: 21, 51). Significant heterogeneity was detected (P<0.0001). Four studies reported patients with SVR who developed a positive HCV viral load that was detected by PCR between 12 and 20 months after stopping IFN treatment (one of 3, three of 11, one of 13, and one of 15 patients converted after being SVR at 6 months). Forty-five (29.6%) of the 152 patients discontinued treatment due to adverse effects. The most common reasons were flu-like symptoms, leukopenia, depression and neurological symptoms. One study was terminated prematurely due to adverse effects.

For genotype 1 patients treated with 3 MU (6 studies), the pooled SVR was 26%.

In a separate analysis in which one outlying study was excluded, the pooled SVR was 31%.

The pooled SVR from 5 studies using IFN treatment for 6 months was 31%.

**IFN dose greater than 3 MU (3 studies, 61 patients).**

The studies suggested that higher doses of IFN did not increase SVR rates and might increase adverse effects. The SVR rates were 27% (at 5 months), 33% and 53%. Rates of withdrawal due to adverse effects were 33% (2 studies) and 35%.

**Authors' conclusions**

Patients undergoing dialysis have a greater SVR to IFN monotherapy than patients with normal renal function.
CRD commentary
The review question was clear in terms of the participants, intervention and outcomes. The inclusion criteria were not defined in terms of the study design. By limiting the search to English language reports listed in only two databases, other relevant studies may have been omitted. Two reviewers independently selected the studies, thus reducing the potential for bias and errors. The methods used to assess validity and extract the data were not described; hence, any efforts made to reduce errors and bias cannot be judged.

The information presented on the included studies was limited. The review authors stated that the data were analysed on an intention-to-treat basis, but no details of the methods used to deal with missing data were provided. The data from 3 MU IFN treatment arms were pooled despite finding significant statistical heterogeneity. Reasons for differences among the studies were not explored and were not discussed. One of the sensitivity analyses was carried out after excluding an outlying study, but reasons for excluding this outlying study were not discussed. Some patients who had a virus response at 6 months were later found to have detectable virus; this may have resulted in an overestimation of the virus response.

The authors’ conclusion compared the response rates of dialysis patients and patients with normal renal function, but the evidence for the reported SVR rates in the latter (normal renal function) was not critically evaluated. In view of the limitations highlighted, the evidence presented was limited and insufficient to support the authors’ conclusions.

Implications of the review for practice and research
Practice: The authors stated that dialysis patients with chronic HCV infection should be identified before kidney transplantation. They stated that clinicians should closely monitor dialysis patients treated with IFN for asthenia, leukopenia and neurotoxicity.

Research: The authors stated that future studies that fully describe the PCR assay and its lower limit of detection, and that assess the HCV RNA level using PCR one year after treatment, are required. They also stated that future studies should assess the dose and duration of IFN treatment.

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