Interferon therapy for HCV-associated glomerulonephritis: meta-analysis of controlled trials

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CRD summary
The authors concluded that standard doses of interferon-based therapy are more effective at improving hepatitis C virus-associated glomerulonephritis than immunosuppressive therapy, but further research is required. The review combined studies of different designs and uncertain quality, which makes it difficult to assess the reliability of these conclusions.

Authors' objectives
To compare antiviral with immunosuppressive therapy for patients with hepatitis C virus (HCV)-associated glomerulonephritis (GN).

Searching
MEDLINE, EMBASE, Current Contents and selected unspecified specialist journals were searched for studies published in English between 1990 and June 2005; the search terms were reported. In addition, the reference lists of reviews and clinical trials were screened. Only peer-reviewed trials published in full were included.

Study selection
Controlled clinical trials (CCTs) that compared antiviral with immunosuppressive therapy for patients with HCV-associated GN were eligible for inclusion. Studies had to report adequate data on treatment response. Studies of patients with positive serology for hepatitis B surface antigen or the human immunodeficiency virus were excluded, as were studies of renal transplant patients. The primary review outcome was the number of patients with a reduction in proteinuria (return to normal or decrease of more than 50%) post-treatment. Secondary outcomes were the number of patients with improved serum creatinine concentration (return to normal or decrease of more than 50%) post-treatment and reduction in proteinuria at follow-up.

In most of the included studies antiviral treatment consisted of subcutaneous interferon alpha (IFN) administered 3 times weekly for at least 6 months. Most immunosuppressive regimens consisted of corticosteroids; one study used corticosteroids plus cyclophosphamide. All patients were anti-HCV antibody seropositive. The mean age of the patients ranged from 46 to 64 years and the proportion of males from 29 to 82%. Where reported, the duration of follow-up ranged from 12 to 71 weeks. The review also assessed tolerance using the drop-out rate.

More than one reviewer selected the studies and any disagreements were resolved by consensus.

Assessment of study quality
The authors did not state that they assessed validity. However, they did report on the adequacy of the randomisation methods.

Data extraction
Results data were extracted on an intention-to-treat basis, and odds ratios (ORs) with 95% confidence intervals (CI) were presented for individual studies.

Two reviewers independently extracted the data, with any discrepancies resolved by consensus. Authors were contacted if required to help eliminate duplicate reports.

Methods of synthesis
Pooled ORs with 95% CIs were calculated using a fixed-effect model and the DerSimonian and Laird random-effects model.
Statistical heterogeneity was assessed using the Cochrane Q test and the $I^2$ statistic. Sensitivity analysis was undertaken.
by only analysing studies that used standard IFN doses (3 x 10^6 UI three times weekly). Publication bias was assessed using a funnel plot.

**Results of the review**

Six CCTs (n=145; 82 patients received antiviral treatment and 63 received immunosuppressive therapy). Of these, two were randomised controlled trials (RCTs, n=66), one was a case-control study (n=19), and the designs of the other studies were not reported.

One RCT appeared to use adequate methods for randomisation.

The drop-out rate after IFN ranged from 0 to 14.2% in three studies.

IFN was associated with a non statistically significant increase in the proportion of patients with a decrease in proteinuria post-treatment compared with immunosuppressive therapy (random-effects OR 1.92, 95% CI: 0.39, 9.57). Significant heterogeneity was detected (p=0.06; I²=53%). There was no evidence of funnel plot asymmetry (p=0.5). For studies that used the standard IFN dose, IFN was associated with a statistically significant increase in the proportion of patients with a decrease in proteinuria post-treatment compared with immunosuppressive therapy (OR 3.86, 95% CI: 1.44, 10.33, p=0.007). No significant heterogeneity was detected (p=0.18; I²=36%). There was evidence of funnel plot asymmetry (p=0.001).

There was no statistically significant difference between IFN and immunosuppressive therapy in the proportion of patients with a post-treatment decrease in serum creatinine. IFN was associated with a significant increase in the proportion of patients with a decrease in proteinuria at follow-up compared with immunosuppressive therapy (fixed-effect OR 6.65, 95% CI: 1.19, 37.14, p=0.03; based on 3 studies). No significant heterogeneity was detected for either of these analyses (p=0.76 and p=0.32, respectively).

**Authors’ conclusions**

Standard doses of IFN-based therapy are more effective at improving HCV-associated GN than immunosuppressive therapy, but further research with newer antiviral agents is required.

**CRD commentary**

The review question was stated clearly. Inclusion criteria for the study design were rather broad. Several relevant sources were searched but no attempts were made to minimise publication or language bias. The potential for publication bias was assessed, but this assessment is of limited value in view of the small number of studies identified. Appropriate methods were used to minimise reviewer error and bias during the review process. Study validity was not adequately assessed, thus the results from these studies and any synthesis may not be reliable. Randomised and non-randomised studies were combined using meta-analysis, but there was no subgroup analysis based on study design. This means that the reliability of the conclusions about efficacy cannot be assessed. Conclusions about the need for further research appear justified.

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

**Practice:** The authors stated that antiviral therapy appears to be the best treatment for active HCV-related GN.

**Research:** The authors stated the need for adequately powered RCTs with sufficient follow-up to evaluate the safety and efficacy of adequate doses of combined antiviral therapy (pegylated IFN plus ribavirin) for patients with HCV-associated GN.

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