Meta-analysis: anti-viral therapy of hepatitis B virus-associated glomerulonephritis

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CRD summary
This review evaluated the efficacy and safety of antiviral therapy in chronic hepatitis B virus-associated glomerulonephritis. Antiviral agents induced remission of the proteinuria and a virological response. These agents seemed well tolerated and did not cause serious adverse events. The authors’ conclusions should be viewed with caution, owing to the small size and poor quality of the studies included.

Authors’ objectives
To evaluate the efficacy and tolerability of antiviral therapy in hepatitis B virus (HBV)-associated glomerulonephritis.

Searching
The Cochrane Library, Current Contents, EMBASE and MEDLINE were searched from June 1980 to December 2005; the search terms were reported. The reference lists of retrieved reviews and published clinical trials were also checked.

Study selection

Study designs of evaluations included in the review
Controlled clinical trials, case-control and cohort studies were eligible for inclusion.

Specific interventions included in the review
The included studies were required to assess primary antiviral therapy. Antiviral therapy included recombinant interferon alfa 2b (r-IFNa 2b) or lamivudine. r-IFNa 2b was used at total weekly doses ranging from 9 to 35 MU (3 to 7 doses per week) for a total treatment period of 4 to 12 months. Lamivudine was given at a dose of 100 mg/day for 49.2 (+/- 16.5) months (1 study).

Participants included in the review
Studies of patients with HBV-associated glomerulonephritis were included. The mean age of the patients ranged from 6.2 to 48.3 years. The majority of the patients had nephrotic syndrome related to membranous glomerulopathy. All patients showed serological evidence of active HBV replication at the beginning of the study. Follow-up after antiviral treatment ranged from 6 to 43.2 months. Studies of patients with functioning renal grafts or studies of previously treated patients were excluded.

Outcomes assessed in the review
The included studies were required to report virological and clinical response. The primary outcome for the review was the remission of proteinuria after antiviral therapy. Secondary end points included drop-out rate and clearance of hepatitis B e antigen (HBeAg) from serum after antiviral therapy.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two independent reviewers extracted the data and any disagreements were resolved by consensus. Data were extracted on the proportion of patients achieving proteinuria remission (<0.3 g/day), the proportion of patients achieving hepatitis B surface antigen (HBsAg) clearance and the proportion of patients dropping out of the study. Investigators were
contacted when necessary to obtain additional data.

Methods of synthesis
How were the studies combined?
The outcomes were analysed on an intention-to-treat basis. Summary estimates and 95% confidence intervals (CIs) were calculated using the random-effects model of DerSimonian and Laird. Publication bias was assessed by the Begg and Mazumadar adjusted rank-correlation test and the Egger regression asymmetry test, and visually using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Cochran Q-test, with a p-value of less than 0.10 considered indicative of statistically significant heterogeneity. The I-squared index and a sensitivity analysis (using a fixed-effect model) were used to estimate the consistency of effects across studies and analytical method. Meta-regression was used to explore possible sources of heterogeneity.

Results of the review
Six clinical trials (82 patients) were included in the review: five (72 patients) assessed r-IFNa 2b and one (10 patients) assessed lamivudine.

Clinical response.
The overall estimates of proteinuria remission and sustained proteinuria remission (at least 6 months after completion of antiviral therapy) for trials of IFN only were 65.2% (95% CI: 52.7, 75.9) and 49.8% (95% CI: 33.3, 60.1), respectively. There was evidence of statistical heterogeneity in the latter data set (p=0.056).

Viral response.
HBeAg clearance was reached in 62.0% (95% CI: 50.5, 72.2) of patients, while HBsAg clearance was achieved in 16.4% (95% CI: 4.7, 44.1); there was evidence of statistical heterogeneity (p=0.005). For trials of IFN only, sustained HBeAg and sustained HBsAg were reached in 50.6% (95% CI: 31.7, 69.4) and 19.8% (95% CI: 5.9, 49.1) of patients, respectively; there was evidence of statistical heterogeneity (p=0.065 and p=0.015, respectively).

Tolerability.
The overall drop-out rate was 12.7% (95% CI: 6.4, 23.6). Six patients discontinued antiviral therapy due to myalgia (n=1) and the high cost of r-IFNa 2b (n=5).

The meta-regression analysis showed a significant association between HBeAg clearance and proteinuria remission after r-IFNa 2b. The effects were similar using random-effects or fixed-effect analyses.

Both the Begg and Mazumadar adjusted rank-correlation test and Egger regression asymmetry test showed a low risk for publication bias.

Authors' conclusions
Antiviral therapy with IFN or lamivudine was effective, safe and well tolerated in HBV-associated glomerulonephritis.

CRD commentary
The review addressed a well-defined question in terms of the participants, interventions, outcomes and study design. Four databases were searched and efforts were made to find further information by reviewing reference lists. The potential influence of publication bias was considered in the report. It was not stated if any language restrictions were applied, therefore language bias can not be ruled out. The authors attempted to minimise bias and errors during the review process by carrying out the data extraction in duplicate. However, it was unclear if the study selection was also performed in duplicate, therefore reviewer error and bias might have been introduced at this stage. No assessment of
study quality was reported, thus the potential impact of methodological flaws in the primary studies upon the reliability of the review findings could not be assessed.

The characteristics of the individual studies, apart from quality, were presented clearly. The overall estimate of proteinuria remission reported in the text was not consistent with that used in the table. Pooling appeared to have been appropriate statistically, and potential sources of heterogeneity were explored using regression analysis. The small number of data sets included might have limited the utility of regression analysis. The authors’ conclusions reflect the data presented, however, as the authors acknowledged, the small number of patients enrolled in the included studies should be taken into consideration.

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

**Practice:** The authors made no specific recommendations for practice.

**Research:** The direct relationship between the rate of proteinuria remission and frequency of membranous nephropathy need to be confirmed in larger series. Issues on cost and lamivudine resistance also need further evaluation.

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