Treatment of hepatitis B virus-associated glomerulonephritis: a meta-analysis

Zhang Y, Zhou JH, Yin XL, Wang FY

CRD summary
The review concluded that antiviral therapy significantly decreased proteinuria and promoted hepatitis B e-antigen clearance in hepatitis B virus-associated glomerulonephritis, but corticosteroids had no significant effect. In paediatric patients, antiviral therapy did not significantly decrease proteinuria. In view of the small included study sizes and uncertainties about their quality, the reliability of the authors’ conclusions is unclear.

Authors' objectives
To evaluate the efficacy and safety of antiviral or corticosteroid treatment for hepatitis B virus-associated glomerulonephritis in adults and children.

Searching
PubMed, EMBASE, the Cochrane Library and CNK (China National Knowledge Infrastructure) were searched to November 2008 for publications in English and Chinese; search terms were reported. The start dates for the searches were not explicitly stated. Bibliographies of each retrieved article, proceedings of major recent meetings on nephrology and hepatology, and related dissertations were handsearched. Only dissertations, conference proceedings, and full text papers published in peer-reviewed journals were included.

Study selection
Controlled clinical trials (CCTs), cohort and case-control studies that evaluated antiviral or corticosteroid treatment for hepatitis B virus-associated glomerulonephritis were eligible for inclusion. Studies of treatment with Chinese herbal medicines were excluded.

The primary outcome was the remission of proteinuria; the secondary outcome was clearance of hepatitis B e-antigen in the serum. Clinical remission was divided into complete remission (proteinuria less than 0.3g/day) and partial remission (reduction in proteinuria).

The antiviral drugs used in the included studies were mainly interferon (mostly recombinant alpha-interferon) and, in fewer studies, lamivudine (at 100mg/day, where reported). The dose of interferon was not clearly reported in general, although more detail was provided for paediatric studies, where dose varied with the weight or height of the child. The antiviral drugs in two adult studies were preceded by two weeks or one month of prednisolone. The intervention in all the studies of corticosteroid treatment was prednisolone (1.5 to 2mg/kg per day in children; 2mg/kg/day or 60mg/day in adults).

Treatment time ranged from four weeks to a mean of 49.2 months (where reported). Controls included no treatment or supportive/symptomatic treatment, using diuretic agents, anti-hypertensives, dipyridamole, fish oil, or angiotensin converting enzyme inhibitors, which were generally also used in the intervention group.

The mean age of included patients in the paediatric studies ranged from 4.5 to 10 years; for the adult studies, the mean age ranged from 20 to 46 years. The overall percentage of males was 76.7%. Approximately half included patients had nephrotic syndrome, and half had membranous nephropathy.

Approximately half of the included studies were conducted in China; the remainder were from Spain, Turkey, South Africa, Taiwan and Thailand.

Two independent reviewers performed the selection, with disagreements resolved via a third reviewer.

Assessment of study quality
It was not clear whether a formal assessment of methodological quality was made. Numbers of drop-outs were reported, along with an apparent quality score for the one randomised controlled trial (RCT).
Data extraction
The numbers of events for each outcome were extracted in order to calculate relative risk (RR) and 95% confidence intervals (CIs). Two independent reviewers performed the data extraction, with disagreements discussed with a third reviewer, who (once a consensus was reached) extracted the relevant data.

Methods of synthesis
Relative risks were pooled using a random-effects model (DerSimonian and Laird) if statistically significant heterogeneity was present, or a fixed-effect model (Mantel-Haenszel) if there was no significant heterogeneity. Between study heterogeneity was determined using the $X^2$ test and the $I^2$ statistic; significant heterogeneity was present if $p$ value was more than 0.10.

Subgroup analyses were performed for paediatric studies, and excluding studies of lamivudine treatment.

Publication bias was assessed using Begg's and Egger's tests, and visually using funnel plots.

Results of the review
Nine studies were identified for the review (n=235 patients), including one randomised controlled trial RCT (n=40 patients; quality score 3) and eight cohort studies (n=195 patients, range 11 to 44). Mean follow-up time ranged from five months to 10 years. There were no drop-outs in six studies; drop-out ranged from 14 to 29% in the remaining three studies. Antiviral therapy was assessed in six studies and corticosteroid treatment in five studies.

Antiviral therapy: The proteinuria remission rate was significantly increased for antiviral therapy versus controls (RR 1.69, 95% CI 1.08 to 2.65; $I^2$=80.5%; six studies). The effect was not changed when the one study of lamivudine treatment was excluded. However, when the analysis was performed for paediatric studies alone, the result was no longer significant (RR 1.40, 95% CI 0.80 to 2.47; $I^2$=79.8%; three studies). All three analyses used a random-effects model due to significant heterogeneity. The clearance rate of hepatitis B e-antigen was significantly higher in the antiviral therapy group compared with control groups (RR 6.44, 95% CI 3.11 to 13.35; $I^2$=42.0%; six studies; fixed-effect model) and also for paediatric patients (RR 10.71, 95% CI 3.74 to 30.63; $I^2$=67.6%; three studies; random-effects model). Kappa analysis showed that proteinuria remission was significantly related to hepatitis B e-antigen clearance after antiviral therapy ($K=0.285$). Fewer antiviral therapy patients (6.38%) than control group patients (17.2%) had renal insufficiency (statistical significance not reported).

Corticosteroid treatment: The proteinuria remission rate was not significantly increased for corticosteroid treatment compared with controls (five studies; random-effects model), but there was significant heterogeneity ($I^2$=80.8%). There was also no significant effect on proteinuria remission rate for paediatric studies alone (three studies; fixed effect model), with no significant heterogeneity ($I^2$=0%).

Some details of adverse events were reported.

The risk of publication bias was reported to be low.

Authors' conclusions
The efficacy and safety of antiviral therapy (including interferon and lamivudine) on hepatitis B virus-associated glomerulonephritis were good. Antiviral therapy was effective on remission of proteinuria and hepatitis B e-antigen clearance, delaying renal function deterioration. However, corticosteroids could not ameliorate hepatitis B virus-associated glomerulonephritis.

CRD commentary
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Some relevant sources were searched, but only in English and Chinese; there was also a restriction in the type of article considered, so some relevant studies could have been missed. However, publication bias was assessed and the risk of bias was found to be low. Efforts were made to reduce error and bias in study selection and data extraction, but it was not clear whether this process applied to study quality assessment.
Some criteria relevant to study quality were assessed, but no details of validity assessment were reported, yet an apparent quality score was provided for the one RCT. Relevant study details were reported. Statistical heterogeneity was assessed and there was evidence for heterogeneity with some outcomes. The statistical method used for the meta-analysis of the RCTs seemed appropriate, but no direct comparisons were made between the two types of treatment. Suitable subgroup analyses were performed.

In view of the small sizes of the included studies and uncertainties about their quality, the reliability of the authors’ conclusions is unclear.

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

**Practice:** The authors stated that corticosteroids alone should not be recommended for hepatitis B virus-associated glomerulonephritis patients, especially those with a high viral load and abnormal liver function. A combination of corticosteroids and antiviral drugs was superior, but viral load should still be closely monitored.

**Research:** The authors identified a need for large scale RCTs of paediatric patients to clarify whether antiviral therapy can induce remission of proteinuria. Trials were also needed to confirm that treatment of hepatitis B virus-associated glomerulonephritis patients with both antiviral drugs and corticosteroids is superior to treatment with corticosteroids alone and also appropriate.

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