World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i6.770

World J Gastroenterol 2010 February 14; 16(6): 770-777
ISSN 1007-9327 (print)

BRIEF ARTICLE

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

Yu Zhang, Jian-Hua Zhou, Xiao-Ling Yin, Feng-Yu Wang

Yu Zhang, Jian-Hua Zhou, Xiao-Ling Yin, Feng-Yu Wang, Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China

Author contributions: Zhang Y designed the research, collected and analyzed the data and wrote the manuscript; Zhou JH designed the research and revised the manuscript; Yin XL and Wang FY participated in the data collection.

Supported by National Natural Science Foundation of China, No. 30772360

Correspondence to: Jian-Hua Zhou, Professor, Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China. jhzhou@tjh.tjmu.edu.cn
Telephone: +86-27-83663256 Fax: +86-27-83663256

Received: October 13, 2009 Revised: December 31, 2009
Accepted: January 7, 2010
Published online: February 14, 2010

Abstract

AIM: To evaluate the efficacy of antiviral or corticosteroid treatment on hepatitis B virus-associated glomerulonephritis (HBV-GN).

METHODS: Six and five trials were used respectively to evaluate the efficacy of either antiviral or corticosteroid treatment on HBV-GN. Pediatric patients were pooled separately to assess their response to the above treatment modalities. The primary and secondary outcomes were remission of proteinuria and clearance of Hepatitis B e-antigen (HBeAg), respectively. A fixed or random effect model was established to collect the data.

RESULTS: The remission rate of proteinuria (RR = 1.69, 95% CI: 1.08-2.65) and the clearance rate of HBeAg (RR = 6.44, 95% CI: 3.11-13.35) were significantly higher in antiviral treatment group than in control group. The proteinuria remission was significantly associated with HBeAg clearance (P = 0.002). However, the difference in proteinuria remission rate was not statistically significant between corticosteroid treatment group and control group (RR = 1.45, 95% CI: 0.68-3.11). Antiviral therapy could significantly promote the HBeAg clearance in pediatric patients, but neither antiviral nor corticosteroid therapy could significantly decrease proteinuria in pediatric patients compared to controls.

CONCLUSION: Antiviral but not corticosteroid treatment can decrease proteinuria and promote HBeAg clearance in HBV-GN patients.

Key words: Hepatitis B virus-associated glomerulonephritis; Drug therapy; Meta-analysis

Peer reviewer: Eva Herrmann, Professor, Department of Internal Medicine, Biomathematics Saarland University, Faculty of Medicine, Kirrberger Str., 66421 Homburg/Saar, Germany

Zhang Y, Zhou JH, Yin XL, Wang FY. Treatment of hepatitis B virus-associated glomerulonephritis: A meta-analysis. *World J Gastroenterol* 2010; 16(6): 770-777 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i6/770.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i6.770

INTRODUCTION

Hepatitis B virus-associated glomerulonephritis (HBV-GN) remains one of the most common secondary glomerular diseases in Chinese children, although its incidence seems to decrease nowadays after the popularization of HBV vaccination[1,2]. Most HBV-GN patients present with nephrotic syndrome and some show mild to moderate proteinuria with hematuria[3]. Although spontaneous remission has been reported in many pediatric patients[3], some still develop progressive renal failure[4-6]. Therefore, it is very important to attenuate proteinuria and slow down renal disease progression in HBV-GN patients.

HBV-GN is treated with either antiviral drugs including interferon, lamivudine, and entecavir or with corticosteroids

and even immunosuppressive agents like mycophenolate mofetil, leflunomide[7,8]. It has been shown that antiviral therapy can promote the clearance of HBV and improve the coexisting renal disease[3], but the efficacy of interferon on HBV-GN has not been confirmed[9,10]. Moreover, interferon therapy is not as successful for HBV-GN in children as for HBV-GN in adults[3]. Thus, the efficacy of antiviral therapy on HBV-GN remains to have been established, especially in pediatric patients. Corticosteroids are also used in treatment of some patients with nephrotic syndrome. However, it is argued that corticosteroid and immunosuppressive agents are unfavorable for HBV-GN since they inhibit the immune system and activate latent HBV, leading to active replication of HBV and deterioration of renal lesions[3,11]. So the efficacy of these treatment modalities on HBV-GN is still uncertain. Up to date, we are not sure if patients with HBV-GN can be treated with antiviral drugs alone and if nephrotic patients can be treated with corticosteroids.

Unfortunately, the data available in studies on HBV-GN treatment are limited and often provide inconsistent results, which can be explained by many factors like variable sample size, racial differences, disease variation as well as interference of other treatment. These inconsistencies can be solved by meta-analysis. In a meta-analysis[12] of antiviral therapy for HBV-GN published in 2006, 2 of the 6 trials included were non-controlled studies, other treatments like corticosteroids and pediatric patients were not analyzed. Thus, we performed a meta-analysis including just controlled trials to evaluate the effects of antiviral drugs and corticosteroids on HBV-GN both in adults and in children.

MATERIALS AND METHODS

Literature search

All eligible articles in English and Chinese published prior to November 2008 were searched from PubMed, EMBASE, Cochrane Library and CNKI. The terms, including hepatitis B virus (or hepatitis B), nephropathy, nephrotic syndrome and therapy, interferon, lamivudine, corticosteroid, prednisolone, *etc.*, were crossed. Furthermore, bibliographies of retrieved articles, proceedings of major recent meetings on nephrology and hepatology and related dissertations in English or Chinese were manually searched.

Criteria for inclusion

Controlled clinical trials, cohort studies, and case-control studies were searched for this systematic review. The diagnosis of HBV-GN was established based on renal pathology. The primary and secondary outcomes were remission of proteinuria and clearance of Hepatitis B e-antigen (HBeAg), respectively. Only dissertations, conference papers and full-text papers published in peer-reviewed journals concerning the treatment of HBV-GN were included in the study. The decision was made based on the quality of studies rather than on their results.

Criteria for exclusion

Publications were excluded if they were non-controlled studies or on treatment of HBV-GN with Chinese herbal drugs. For serial reports of the same patients, only those who provided the most comprehensive information were included.

Definition of treatment effect

The assessed outcomes included clinical and virologic responses. Clinical responses were divided into complete remission and partial remission, which were respectively defined as disappearance of proteinuria (< 0.3 g/d) and reduction in urine protein excretion. Virologic response was defined as clearance of HBeAg from serum.

Data extraction and quality assessment

Two reviewers independently selected the studies, and extracted data and outcomes according to the inclusion criteria. In case of disagreement between the two reviewers, a third reviewer was introduced to discuss with the two reviewers and extracted the data when all the three reviewers reached a consensus.

Statistical analysis

Meta-analysis was performed using fixed-effect or random-effect methods, depending on the absence or presence of significant heterogeneity. Statistical heterogeneity between trials was evaluated by the Cochran χ^2 test and significance was considered when $P < 0.10$. In the absence of statistically significant heterogeneity, the Mantel-Haenszel method in the fixed-effect model was used for meta-analysis. Otherwise, the DerSimonian and Laird method[13] in the random-effect model was selected. The relative risk (RR) with 95% confidence interval (CI) was used to assess the treatment efficacy. The combined result was an average RR and 95% CI weighted according to the standard error of the RR of the trial. $P < 0.05$ was considered statistically significant. We used funnel plots to assess the publication bias, and tested for funnel plot asymmetry using Egger's test[14] and Begg's test[15]. All analyses were performed with STATA version 9.0 (Stata Corp, College Station, Tx) and Review Manager version 4.2 (RevMan, Cochrane Collaboration, Oxford, England).

RESULTS

Description of included trials in the meta-analysis

Of the 998 studies we identified in the search, 55 and 943 articles were published in English and Chinese, respectively. After a review of the titles and abstracts or full texts, 989 articles were excluded and 9 articles[16-24] (8 in English and 1 in Chinese) were included based on the pre-specified criteria. One of them was randomized controlled trial (RCT)[16], others were cohort studies. Among the 9 articles, 5 (55.6%) were from China, corresponding to the high incidence of HBV-GN in China and the low incidence in Europe and North American. The characteristics of 9 clinical trials included are shown in Table 1, and the details of intervention methods like dose and duration of drugs, main outcomes, and follow-up time in each study are provided in Tables 2 and 3.

Table 1 Characteristics of 9 included studies

Study	Country or region	Patients		Study design
		Gender	Age (yr)	
Lin[16], 1995	Taiwan, China	29M, 11F	6.2 ± 2.4	RCT (3 score)
Bhimma *et al*[17], 2002	South Africa	34M, 5F	8.7, 9.2	Cohort study
Lai *et al*[18], 1991	Hong Kong, China	14M, 2F	27.2 ± 6.2	Cohort study
Tang *et al*[19], 2005	Hong Kong, China	14M, 8F	48.3 ± 12.8, 43.1 ± 22.8	Cohort study
Panomsak *et al*[20], 2006	Thailand	14M, 10F	39.8	Cohort study
Yang *et al*[21], 2003	Wenzhou, China	28M, 5F	8.01 ± 1.23	Cohort study
Lai *et al*[22], 1990	Hong Kong, China	10M, 5F	22.8 ± 14.4, 17.2 ± 8.2	Cohort study
Ozdamar *et al*[23], 2003	Turkey	11M, 3F	10	Cohort study
Peña *et al*[24], 2001	Spain	11M, 1F	4.52 ± 2.34	Cohort study

RCT: Randomized controlled trial.

Table 2 Design of 6 clinical trials on efficacy of antiviral therapy for HBV-GN

Author	Group	Case (*n*)	Intervention	Dropped-out (*n*)	Outcome			Follow-up
					CR	VR	Renal insufficiency (*n*)	
Lin[16], 1995	Control	20	The same supportive treatment as treatment group	0	7 complete remission, 10 partial remission	0 HBeAg clearance	UA	24 mo
	Treatment	20	rIFNα, 5 mU (weight < 20 kg), 8 mU (weight ⩾ 20 kg), 3 t/w for 12 mo	0	20 complete remission	16 HBeAg clearance	UA	
Bhimma *et al*[17], 2002	Control	20	Anti-hypertension and diuretics if needed	0	0 complete remission, 5 partial remission	1 HBeAg clearance	0	40 wk
	Treatment	24	rIFNα-2b, 10 mU/m^2, 3 t/w for 16 wk	5	10 complete remission, 4 partial remission	10 HBeAg clearance, 4 reverters, 5 failures	2	
Lai *et al*[18], 1991	Control	11	Diuretic agents or dipyridamole or none	0	0 complete remission, 8 partial remission	0 HBeAg clearance	4	60 mo
	Treatment	5	2 wk of prednisolone 40 mg/d followed by 12 wk of rIFNα-2b 3 mU, 3 t/w	0	1 complete remission, 4 partial remission	1 HBeAg seroconversion	1	
Tang *et al*[19], 2005	Control	12	ACEI or ARB	0	2 complete remission, 2 partial remission	1 HBeAg clearance, 2 HBeAg seroconversion	5 ESRD	49.2 ± 16.5 mo
	Treatment	10	3TC, 100 mg/d, 49.2 ± 16.5 mo, plus ACEI or ARB	0	7 complete remission, 3 partial remission	8 HBV-DNA clearance (5 HBeAg clearance)	0	
Panomsak *et al*[20], 2006	Control	10	ACEI, fish oil, or neither	3	2 complete remission	0 HBeAg clearance	2 ESRD	5-120 mo
	Treatment	7	1 month of prednisolone followed by 3TC in 6 case and IFNα in one case	0	2 complete remission, 5 partial remission	1 HBeAg seroconversion	0	
Yang *et al*[21], 2003	Control	14	The supportive or symptomatic treatment	0	9 complete remission, 2 partial remission	3 HBeAg seroconversion	0	3.8 ± 2.4 yr
	Treatment	6	rIFNα, 1-3 mU, 3 t/w for 3-6 mo	0	3 complete remission, 2 partial remission	3 HBeAg seroconversion	0	

HBV-GN: Hepatitis B virus-associated glomerulonephritis; CR: Clinical response; VR: Virologic response; UA: Unavailable; 3TC: Lamivudine; rIFNα: Recombinant α-interferon; HBeAg: Hepatitis B e-antigen; ACEI: Angiotension converting enzyme inhibitors; ARB: Angiotensin Ⅱ receptor blocker; ESRD: End-stage renal disease; t/w: Times per week.

Therapeutic evaluation: Antiviral therapy

The efficacy of antiviral therapy on HBV-GN was assessed using 6 trials[16-21], including 1 RCT[16] and 5 cohort studies[17-21]. The total number of patients was 159 (72 in treatment group with 5 dropped out, 87 in control group with 3 dropped out). Among the 159 patients, 133 presented with nephrotic syndrome and 134 with membranous nephropathy. The mean follow-up time was five months to ten years, significantly different between trials.

Clinical response in antiviral treatment group and control group: The χ^2 test of heterogeneity was highly significant ($P = 0.0001$). Accordingly, a random-effect model was used. The remission rate of proteinuria was significantly higher in antiviral treatment group (91.0%) than in control group (56.0%) with a combined RR of 1.69 (95% CI: 1.08-2.65, Figure 1A). The result of sensitivity analysis remained unchanged even if lamivudine treatment studies were excluded (RR = 1.50, 95% CI: 0.99-2.26, Figure 1B), indicating that the result is stable.

Furthermore, three trials[16,17,21] on pediatric patients were analyzed. The χ^2 test of heterogeneity was also highly significant ($P = 0.007$), so a random-effect model was selected. As shown in Figure 1C, the remission rate

Table 3 Design of 5 clinical trials on efficacy of corticosteroid therapy for HBV-GN

Author	Group	Case (*n*)	Intervention	Dropped-out (*n*)	Outcome		Follow-up
					CR	Renal insufficiency (*n*)	
Lai *et al*[22], 1990	Control	7	Diuretic agents	0	2 complete remission	UA	14-37 mo
	Treatment	8	Prednisolone 60 mg/d (adult), 40 mg/m^2 per day (< 15 yr), for 6 mo	0	3 complete remission, 4 partial remission, 1 relapse	UA	
Ozdamar *et al*[23], 2003	Control	4	None	0	4 complete remission	UA	5-120 mo
	Treatment	8	Prednisolone, 2 mg/kg per day	2	1 complete remission, 4 partial remission, 1 death due to sepsis	UA	
Panomsak *et al*[20], 2006	Control	10	ACEI, fish oil, or neither	3	2 complete remission	2 ESRD	5-120 mo
	Treatment	6	Prednisolone, 2 mg/kg per day	1	3 complete remission, 2 partial remission	0	
Yang *et al*[21], 2003	Control	14	The same supportive and symptomatic treatment as treatment group	0	9 complete remission, 2 partial remission	0	3.8 ± 2.4 yr
	Treatment	8	Prednisolone, 1.5-2 mg/kg per day, for 3 mo	0	4 complete remission, 2 partial remission	0	
Peña *et al*[24], 2001	Control	4	Symptomatic treatment	0	4 complete remission	UA	9.95 ± 5.88 yr
	Treatment	7	Prednisone, 1.5-2 mg/kg per day, a minimun of 4 wk (1 case prednisone + CTX)	0	7 steroid-resistant during therapy, but all complete remission at the end of follow-up	UA	

CTX: Cytoxan.

of proteinuria in pediatric patients was slightly higher in treatment group (86.7%) than in control group (61.1%) with a combined RR of 1.40 (95% CI: 0.80-2.47), but the difference was not statistically significant ($P = 0.24$).

Virologic response in antiviral treatment group and control group: The χ^2 test of heterogeneity was not significant ($P = 0.13$), therefore a fixed-effect model was selected. The clearance rate of HBeAg was significantly higher in antiviral treatment group (59.7%) than in control group (8.33%) with a RR of 6.44 (95% CI: 3.11-13.35, Figure 2A).

In addition, 3 trials[16,17,21] on pediatric patients were separately analyzed for virologic response. The χ^2 test of heterogeneity was significant ($P = 0.05$), therefore a random-effect model was used. The clearance rate of HBeAg was significantly higher in antiviral treatment group (73.3%) than in control group (7.4%) with a RR of 10.71 (95% CI: 3.74-30.63, Figure 2B).

Consistency analysis of clinical and virologic responses: Kappa analysis showed that proteinuria remission was significantly related with HBeAg clearance after antiviral therapy (kappa = 0.285, $P = 0.002$)

Effect of antiviral therapy on protection of renal function

The renal function of patients was observed in 5 of the 6 trials during the follow-up (Table 2). Renal insufficiency was found in only 3 of 47 (6.38%) patients in the antiviral treatment group and in 11 of 64 (17.2%) patients in the control group, respectively.

Therapeutic evaluation: Corticosteroid treatment

The efficacy of corticosteroid treatment on HBV-GN was assessed in 5 out of 9 articles[20-24]. Two of them were included in meta-analysis of antiviral therapy efficacy. Of the 23 patients in Panomsak's study[20], 7, 6 and 10 were treated with antiviral drugs, prednisolone and symptomatic treatment, respectively. Of the 28 patients in Yang's study[21], 6, 8 and 14 were treated with antiviral drugs, prednisolone and symptomatic treatment, respectively. All the 5 trials were cohort studies. The clinical response at the end of follow-up is shown in Figure 3A. Of the 76 patients analyzed, 37 were in corticosteroid treatment group with 3 dropped out, 39 were in control group with 3 dropped out. Among them, 52 presented with nephrotic syndrome and 56 with membranous nephropathy. The χ^2 test of heterogeneity was highly significant ($P = 0.001$), so a random-effect model was used. The combined RR was 1.45 with a 95% CI of 0.68-3.11 ($P = 0.34$), indicating that there is no significant difference in proteinuria remission rate between corticosteroid treatment group and control group. However, this result should be carefully interpreted since a limited number of clinical trials can affect the conclusion of meta-analysis. Besides, it was difficult to assess the protective effect of corticosteroid treatment on renal function since only 2 of 5 clinical trials described the renal function during the followed-up.

Moreover, 3 trials[21,23,24] on pediatric patients were separately pooled to analyze the efficacy of corticosteroid treatment. The χ^2 test of heterogeneity was not significant ($P = 0.61$), so a fixed-effect model was used. The combined RR was 0.91 with a 95% CI of 0.65-1.27 ($P = 0.58$), indicating that the difference in the remission rate of proteinuria was also not significant between corticosteroid treatment group and control group (Figure 3B).

Publication bias

Publication bias may exist when no significant findings remain unpublished, thus artificially inflating the apparent magnitude of an effect. Egger and Begg tests showed that the risk of having missed trials was acceptably low, since the *P* values for the clinical and virologic responses to antiviral therapy and the clinical response to corticosteroid

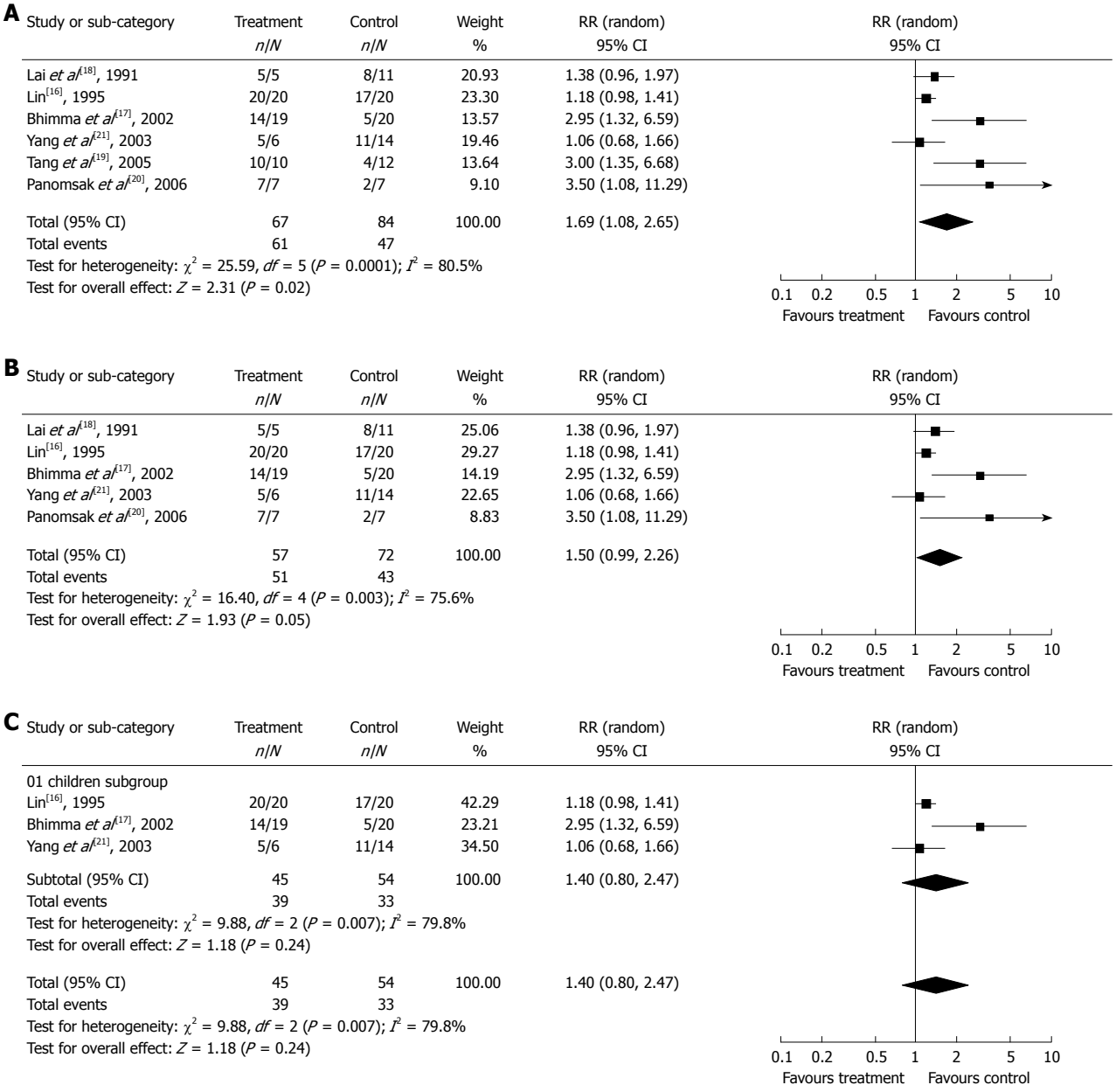


Figure 1 Proteinuria remission rate in antiviral treatment group and control group (A, B) and in pediatric patients (C).

treatment were greater than 0.05. The funnel plots of study results against precision are shown in Figure 4.

Adverse events

Since adverse events were reported inconsistently in across studies and the relevant information in these studies was incomplete, we did not evaluate their incidence and severity of adverse events of these drugs. Some adverse events such as influenza-like illness, anemia, leucopenia, *etc*, were reported in patients treated with IFN. Almost all patients showed good tolerance to long-term administration of lamivudine, although some patients complained of headache, dizziness, local myalgia, paresthesia, *etc*.

DISCUSSION

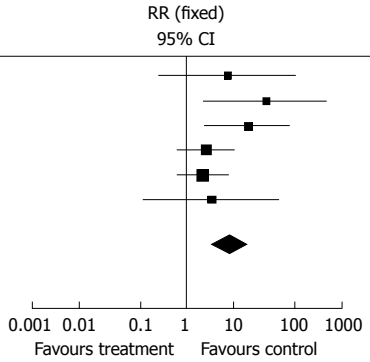
Most HBV-GN patients presented with nephrotic syndrome, many of them, especially pediatric patients showed a spontaneous remission trend, so whether the patients should be treated with antiviral drugs or with immunosuppressive agents remains to be elucidated. Antiviral therapy has been recommended in many studies for HBV-GN since it can effectively inhibit HBV replication and attenuate proteinuria[9,25-33]. Our results demonstrated that antiviral therapy could significantly improve the remission rate of proteinuria, the clearance rate of HBeAg, and renal progression. Moreover, Kappa analysis showed that proteinuria remission is significantly related with HBeAg clearance after antiviral therapy. Only 5 patients were dropped out in antiviral treatment group due to economical reasons. Almost all patients were tolerable to antiviral drugs. Our results are consistent with Fabrizi's study[12]. Since each trial used different kinds, dosages and treatment courses of antiviral drugs, the

A

Study or sub-category	Treatment *n/N*	Control *n/N*	Weight %	RR (fixed) 95% CI
Lai *et al*[18], 1991	1/5	0/11	4.88	6.00 (0.29, 126.30)
Lin[16], 1995	16/20	0/20	7.32	33.00 (2.11, 515.02)
Bhimma *et al*[17], 2002	14/19	1/20	14.26	14.74 (2.14, 101.44)
Yang *et al*[21], 2003	3/6	3/14	26.34	2.33 (0.65, 8.42)
Tang *et al*[19], 2005	5/10	3/12	39.90	2.00 (0.63, 6.38)
Panomsak *et al*[20], 2006	1/7	0/7	7.32	3.00 (0.14, 63.15)
Total (95% CI)	67	84	100.00	6.44 (3.11, 13.35)
Total events	40	7		

Test for heterogeneity: $\chi^2 = 8.62$, $df = 5$ ($P = 0.13$); $I^2 = 42.0\%$

Test for overall effect: $Z = 5.01$ ($P < 0.00001$)



B

Study or sub-category	Treatment *n/N*	Control *n/N*	Weight %	RR (fixed) 95% CI
01 children subgroup				
Lin[16], 1995	16/20	0/20	15.27	33.00 (2.11, 515.02)
Bhimma *et al*[17], 2002	14/19	1/20	29.76	14.74 (2.14, 101.44)
Yang *et al*[21], 2003	3/6	3/14	54.97	2.33 (0.65, 8.42)
Subtotal (95% CI)	45	54	100.00	10.71 (3.74, 30.63)
Total events	33	4		

Test for heterogeneity: $\chi^2 = 6.17$, $df = 2$ ($P = 0.05$); $I^2 = 67.6\%$

Test for overall effect: $Z = 4.42$ ($P < 0.00001$)

Total (95% CI)	45	54	100.00	10.71 (3.74, 30.63)
Total events	33	4		

Test for heterogeneity: $\chi^2 = 6.17$, $df = 2$ ($P = 0.05$); $I^2 = 67.6\%$

Test for overall effect: $Z = 4.42$ ($P < 0.00001$)

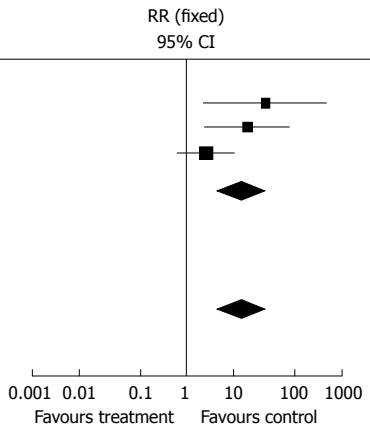


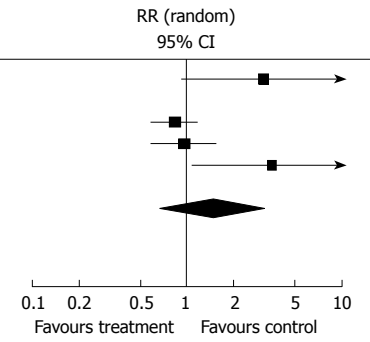
Figure 2 Clearance rate of HBeAg in antiviral treatment group and control group (A) and in pediatric patients (B).

A

Study or sub-category	Treatment *n/N*	Control *n/N*	Weight %	RR (random) 95% CI
Lai *et al*[22], 1990	7/8	2/7	18.57	3.06 (0.92, 10.17)
Peña *et al*[24], 2001	7/7	4/4		Not estimable
Ozdamar *et al*[23], 2003	5/6	4/4	32.12	0.83 (0.58, 1.19)
Yang *et al*[21], 2003	6/8	11/14	30.32	0.95 (0.59, 1.55)
Panomsak *et al*[20], 2006	5/5	2/7	18.99	3.50 (1.08, 11.29)
Total (95% CI)	34	36	100.00	1.45 (0.68, 3.11)
Total events	30	23		

Test for heterogeneity: $\chi^2 = 15.62$, $df = 3$ ($P = 0.001$); $I^2 = 80.8\%$

Test for overall effect: $Z = 0.96$ ($P = 0.34$)



B

Study or sub-category	Treatment *n/N*	Control *n/N*	Weight %	RR (fixed) 95% CI
01 children subgroup				
Peña *et al*[24], 2001	7/7	4/4		Not estimable
Ozdamar *et al*[23], 2003	5/6	4/4	37.50	0.83 (0.58, 1.19)
Yang *et al*[21], 2003	6/8	11/14	62.50	0.95 (0.59, 1.55)
Suntotal (95% CI)	21	22	100.00	0.91 (0.65, 1.27)
Total events	18	19		

Test for heterogeneity: $\chi^2 = 0.27$, $df = 1$ ($P = 0.61$); $I^2 = 0\%$

Test for overall effect: $Z = 0.56$ ($P = 0.58$)

Total (95% CI)	21	22	100.00	0.91 (0.65, 1.27)
Total events	18	19		

Test for heterogeneity: $\chi^2 = 0.27$, $df = 1$ ($P = 0.61$); $I^2 = 0\%$

Test for overall effect: $Z = 0.56$ ($P = 0.58$)

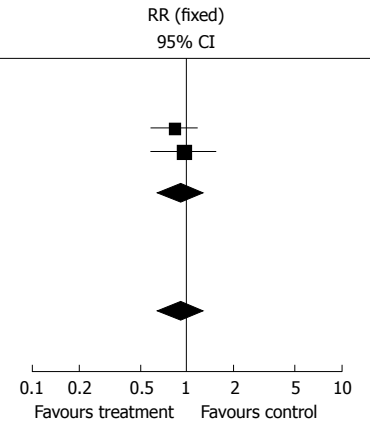


Figure 3 Proteinuria remission rate in corticosteroid treatment group and control group (A) and in pediatric patients (B).

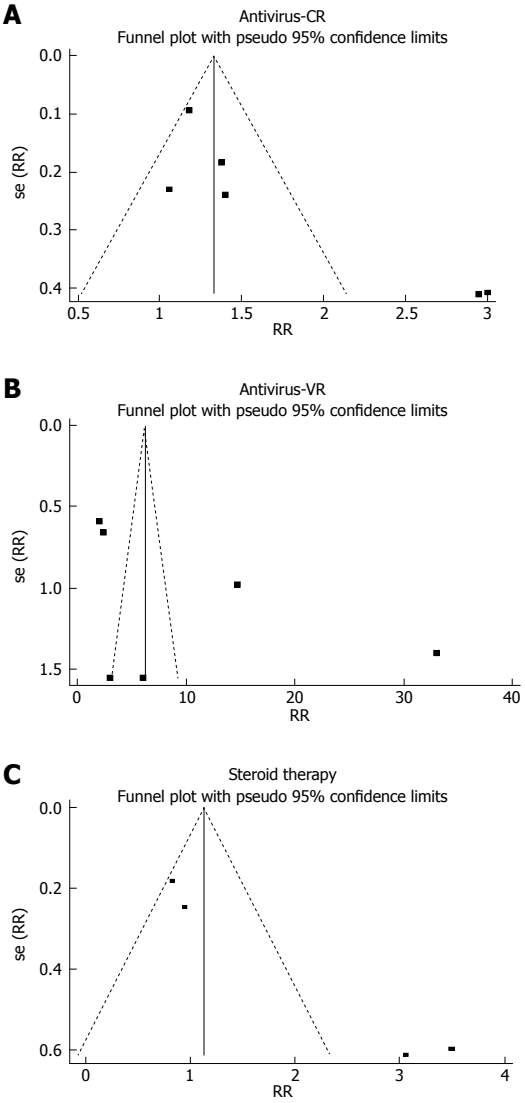


Figure 4 Funnel plots for 6 articles in meta-analysis of clinical response to antiviral therapy (A), 6 articles in meta-analysis of virologic response to antiviral therapy (B), and 5 articles in meta-analysis of clinical response to corticosteroid treatment (C).

meta-analysis proved the efficacy of antiviral treatment but did not necessarily mean that an exact treatment protocol should be recommended. The meta-analysis of pediatric patients showed that antiviral therapy could significantly increase the clearance rate of HBeAg, but not remarkably improve proteinuria, which is not consistent with our above findings possibly due the limited sample size. Large-scale randomized controlled trials on pediatric patients are needed to clarify if antiviral therapy can induce remission of proteinuria.

Corticosteroid is the first-line drug for idiopathic nephrotic syndrome, but it may activate potent HBV infection leading to deterioration of liver and renal lesion[22,34-36]. Our meta-analysis showed that corticosteroid treatment could not significantly improve proteinuria. The effect of corticosteroids on proteinuria remission was not better than nonspecific symptomatic treatment, but its potent risk could not be neglected. Therefore, based on the results of this meta-analysis, corticosteroid should not be recommended for HBV-GN patients solely, especially for those with a high viral load and abnormal liver functions. Theoretically, corticosteroid in combination with antiviral drugs is certainly superior over corticosteroid alone, but no trials are available. So corticosteroid may only be used cautiously on the basis of antiviral therapy with viral load closely monitored.

As with all meta-analyses, our study had certain limitations of publication bias[37]. The number of high-quality clinical trials and enrolled patients was limited in this study. Moreover, the time of treatment was not long enough to evaluate its effects on chronic HBV-GN.

In conclusion, the efficacy and safety of antiviral therapy (including IFN and lamivudine) on HBV-GN are good. Antiviral therapy is effective on remission of proteinuria, and HBeAg clearance, delaying renal function deterioration. However, corticosteroids cannot ameliorate HBV-GN.

COMMENTS

Background

Hepatitis B virus-associated glomerulonephritis (HBV-GN) is one of the common secondary glomerular diseases in China. Although spontaneous remission can occur in many pediatric patients, some still develop progressive renal failure. Therefore, it is very important to attenuate proteinuria and delay renal disease progression.

Research frontiers

So far HBV-GN has been treated like hepatitis B with antiviral drugs including interferon, lamivudine, entecavir or like primary nephrotic syndrome with corticosteroids and even immunosuppressive agents such as mycophenolate mofetil, leflunomide, *etc*. However, it is still uncertain up to now about the efficacy of these treatment modalities.

Innovations and breakthroughs

The data available in previous studies on HBV-GN treatment are limited and often provide inconsistent results. So far only one meta-analysis of antiviral therapy for HBV-GN was published in 2006, but 2 of the 6 trials included were non-controlled studies. The meta-analysis including controlled studies is the first to evaluate the effects of antiviral drugs and corticosteroids on HBV-GN. Moreover, pediatric patients were separately assessed.

Applications

The results of this study suggest that antiviral but not corticosteroid treatment can decrease proteinuria and promote Hepatitis B e-antigen clearance in HBV-associated glomerulonephritis patients. It may help doctors to optimally treat HBV-GN patients.

Terminology

Hepatitis B virus-associated glomerulonephritis is an immune-mediated secondary glomerular disease characterized by deposits of hepatitis B viral antigens, immunoglobulins and C3 in the glomerular capillary wall and mesangium. Nephrotic syndrome, proteinuria and/or hematuria are the most common renal manifestations.

Peer review

The present manuscript describes a meta-analysis for the evaluation of clinical and virologic responses to antiviral and corticosteroid treatment of hepatitis B-associated nephritis. Overall, the methods are appropriate and the results are believable.

REFERENCES

1 **Bhimma R**, Coovadia HM, Adhikari M, Connolly CA. The impact of the hepatitis B virus vaccine on the incidence of hepatitis B virus-associated membranous nephropathy. *Arch Pediatr Adolesc Med* 2003; **157**: 1025-1030

2 **Xu H**, Sun L, Zhou LJ, Fang LJ, Sheng FY, Guo YQ. The effect of hepatitis B vaccination on the incidence of childhood HBV-

associated nephritis. *Pediatr Nephrol* 2003; **18**: 1216-1219
3 **Walters S**, Levin M. Infectious diseases and the kidney. In: Barratt TM, Avner ED, Harmon WE, editors. Pediatric Nephrology. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1999: 1088-1090
4 **Lai KN**, Lai FM, Chan KW, Chow CB, Tong KL, Vallance-Owen J. The clinico-pathologic features of hepatitis B virus-associated glomerulonephritis. *Q J Med* 1987; **63**: 323-333
5 **Gilbert RD**, Wiggelinkhuizen J. The clinical course of hepatitis B virus-associated nephropathy. *Pediatr Nephrol* 1994; **8**: 11-14
6 **Lin CY**. Hepatitis B virus-associated membraneous nephropathy: clinical features, immunological profiles and outcome. *Nephron* 1990; **55**: 37-44
7 **Bhimma R**, Coovadia HM. Hepatitis B virus-associated nephropathy. *Am J Nephrol* 2004; **24**: 198-211
8 **Zhou JH**, Zhang Y. Treatment of Hepatitis B Virus Associated Nephritis in Children. *Shiyong Erke Linchuang Zazhi* 2008; **23**: 329-332
9 **Chung DR**, Yang WS, Kim SB, Yu E, Chung YH, Lee Y, Park JS. Treatment of hepatitis B virus associated glomerulonephritis with recombinant human alpha interferon. *Am J Nephrol* 1997; **17**: 112-117
10 **Wong SN**, Yu EC, Lok AS, Chan KW, Lau YL. Interferon treatment for hepatitis B-associated membranous glomerulonephritis in two Chinese children. *Pediatr Nephrol* 1992; **6**: 417-420
11 Appel GB, Radhakrishnan J, D'Agati V. Secondary glomerular disease. In: Brenner BM, editor. The Kidney. 6th ed. Philadelphia, PA: WB Saunders, 2000: 1411
12 **Fabrizi F**, Dixit V, Martin P. Meta-analysis: anti-viral therapy of hepatitis B virus-associated glomerulonephritis. *Aliment Pharmacol Ther* 2006; **24**: 781-788
13 **DerSimonian R**, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177-188
14 **Egger M**, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629-634
15 **Begg CB**, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088-1101
16 **Lin CY**. Treatment of hepatitis B virus-associated membranous nephropathy with recombinant alpha-interferon. *Kidney Int* 1995; **47**: 225-230
17 **Bhimma R**, Coovadia HM, Kramvis A, Adhikari M, Kew MC. Treatment of hepatitis B virus-associated nephropathy in black children. *Pediatr Nephrol* 2002; **17**: 393-399
18 **Lai KN**, Li PK, Lui SF, Au TC, Tam JS, Tong KL, Lai FM. Membranous nephropathy related to hepatitis B virus in adults. *N Engl J Med* 1991; **324**: 1457-1463
19 **Tang S**, Lai FM, Lui YH, Tang CS, Kung NN, Ho YW, Chan KW, Leung JC, Lai KN. Lamivudine in hepatitis B-associated membranous nephropathy. *Kidney Int* 2005; **68**: 1750-1758
20 **Panomsak S**, Lewsuwan S, Eiam-Ong S, Kanjanabuch T. Hepatitis-B virus-associated nephropathies in adults: a clinical study in Thailand. *J Med Assoc Thai* 2006; **89** Suppl 2: S151-S156
21 **Yang Q**, Zhuang JQ, Lin RX, Yang YZ, Wang ZX. Clinico-pathological Features and Treatment of Hepatitis B Virus Associated Membranous Nephropathy in Children. *Zhongguo Zhongxiyi Jiehe Shenbing Zazhi* 2003; **4**: 706-708
22 **Lai KN**, Tam JS, Lin HJ, Lai FM. The therapeutic dilemma of the usage of corticosteroid in patients with membranous nephropathy and persistent hepatitis B virus surface antigenaemia. *Nephron* 1990; **54**: 12-17
23 **Ozdamar SO**, Gucer S, Tinaztepe K. Hepatitis-B virus associated nephropathies: a clinicopathological study in 14 children. *Pediatr Nephrol* 2003; **18**: 23-28
24 **Peña A**, Débora MJ, Melgosa M, Luz Picazo M, Navarro M. Membranous nephropathy associated with hepatitis B in Spanish children. *Clin Nephrol* 2001; **55**: 25-30
25 **Shapiro RJ**, Steinbrecher UP, Magil A. Remission of nephrotic syndrome of HBV-associated membranous glomerulopathy following treatment with interferon. *Am J Nephrol* 1995; **15**: 343-347
26 **Kavukçu S**, Başdemir G, Eroğlu Y, Türkmen M, Eser F, Büyükgebiz B. Interferon treatment in hepatitis B virus-associated membranous glomerulopathy. *Pediatr Nephrol* 1995; **9**: 539-540
27 **Conjeevaram HS**, Hoofnagle JH, Austin HA, Park Y, Fried MW, Di Bisceglie AM. Long-term outcome of hepatitis B virus-related glomerulonephritis after therapy with interferon alfa. *Gastroenterology* 1995; **109**: 540-546
28 **Connor FL**, Rosenberg AR, Kennedy SE, Bohane TD. HBV associated nephrotic syndrome: resolution with oral lamivudine. *Arch Dis Child* 2003; **88**: 446-449
29 **Filler G**, Feber J, Weiler G, Le Saux N. Another case of HBV associated membranous glomerulonephritis resolving on lamivudine. *Arch Dis Child* 2003; **88**: 460
30 **Gan SI**, Devlin SM, Scott-Douglas NW, Burak KW. Lamivudine for the treatment of membranous glomerulopathy secondary to chronic Hepatitis B infection. *Can J Gastroenterol* 2005; **19**: 625-629
31 **Kanaan N**, Horsmans Y, Goffin E. Lamivudine for nephrotic syndrome related to hepatitis B virus (HBV) infection. *Clin Nephrol* 2006; **65**: 208-210
32 **Okuse C**, Yotsuyanagi H, Yamada N, Ikeda H, Takahashi H, Suzuki M, Kondo S, Kimura K, Koike J, Itoh F. Successful treatment of hepatitis B virus-associated membranous nephropathy with lamivudine. *Clin Nephrol* 2006; **65**: 53-56
33 **Wen YK**, Chen ML. Remission of hepatitis B virus-associated membranoproliferative glomerulonephritis in a cirrhotic patient after lamivudine therapy. *Clin Nephrol* 2006; **65**: 211-215
34 **Taskapan H**, Oymak O, Dogukan A, Ozbakir O, Utas C. Transformation of hepatitis B virus-related membranous glomerulonephritis to crescentic form. *Clin Nephrol* 2000; **54**: 161-163
35 **Lai FM**, Tam JS, Li PK, Lai KN. Replication of hepatitis B virus with corticosteroid therapy in hepatitis B virus related membranous nephropathy. *Virchows Arch A Pathol Anat Histopathol* 1989; **414**: 279-284
36 **Lin CY**. Clinical features and natural course of HBV-related glomerulopathy in children. *Kidney Int Suppl* 1991; **35**: S46-S53
37 **Thornton A**, Lee P. Publication bias in meta-analysis: its causes and consequences. *J Clin Epidemiol* 2000; **53**: 207-216

S- Editor Tian L **L- Editor** Wang XL **E- Editor** Lin YP