Treatment of Hepatitis B Virus-Associated Nephropathy

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Key Words

Hepatitis B virus · Nephropathy · Antiviral therapy · Immunosuppressive therapy

Abstract

Epidemiological studies have shown a relationship between hepatitis B virus (HBV) infection and development of proteinuria in some patients (most commonly children), with a predominance for male gender and histological findings of membranous nephropathy on renal biopsy. The presence of immune complexes in the kidney suggests an immune complex basis for the disease, but a direct relation between HBV and membranous nephropathy (or other types of glomerular diseases) remains to be proven. Clearance of HBV antigens, either spontaneous or following antiviral treatments results in improvement in proteinuria. Thus, prompt recognition and specific antiviral treatment are critical in managing patients with HBV and renal involvement. The present review focuses on treatment of HBV with special emphasis given to antiviral therapies, its complications, and dosing in patients with HBV-associated kidney disease.

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Introduction

Approximately one third of the world's population has serological evidence of past or present infection with hepatitis B virus (HBV), and 350 million people are chronically infected, making it one of the most common human pathogens [1, 2]. The spectrum of disease and natural history of chronic HBV infection is diverse and variable, ranging from a low viremic inactive carrier state to progressive chronic hepatitis, which may evolve to cirrhosis and hepatocellular carcinoma.

Renal involvement is among its most common extra-hepatic manifestations and usually manifests in the form of immune complex mediated glomerulopathy, such as membranoproliferative glomerulonephritis [3–5], focal segmental glomerulosclerosis, minimal change disease [6, 7], lupus nephritis [8, 9], and IgA nephropathy [10, 11]. However, the most common association is with membranous nephropathy (MN), especially in children, and it is in this regard that the term HBV-associated nephropathy is most commonly used. However, with exception of MN, it is likely that the reports of other forms of glomerular disease in patients with HBV reflect mainly incidental findings [6, 12–19].

Table 1. Phases of hepatitis B infection

Phase	HBeAg	ALT	HBV DNA
Immune tolerance	+	normal	very high
HBeAg-positive hepatitis	+	abnormal	high
Inactive carrier	–	normal	low/undetectable
HBeAg-negative hepatitis	–	abnormal	high

An example of the potential incidental findings can be given regarding IgA nephropathy. Lai et al. [11, 20, 21] examined the ability of HBV antigenemia in inducing IgA nephropathy in patients with IgA nephropathy with no previous history of liver diseases and normal liver function tests. All were HBsAg and anti-HBcAg positive with high titers. Immunoperoxidase studies using monospecific polyclonal antibodies revealed HBcAg and HBsAg in the nuclei and cytoplasm of glomerular mesangial cells in the majority of patients. The authors concluded that immune complexes involving HBcAg and HBsAg may induce IgA nephropathy in persons who carry HBV. It is, however, unclear whether IgA nephropathy is a ‘complication’ of HBV infection or merely a coincidental association in countries where both HBV and IgA nephropathy are common, e.g. China, where nationwide cross-sectional seroepidemiological study in the 1990s showed that approximately 60% of the population had a history of HBV infection, and 9.8% of persons were chronically infected with HBV [22], and at the same time, IgA nephropathy is the most common form of a glomerular disease in this population [23]. The pathogenesis of HBV-associated nephropathy, including potential immunopathogenetic mechanisms, biosocial background and genetic factors has been the subject of a recent review [24]. The diagnosis of HBV-mediated glomerular disease requires detection of the virus in the blood and the exclusion of other causes of glomerular diseases.

Natural History

Subjects with chronic HBV infection can be divided into two groups: HBeAg positive and negative (table 1). In most cases, chronic HBV infection begins with positive HBeAg, which classically is a marker of active viral replication. Many HBeAg-positive children and adolescents have normal liver enzymes despite high levels of HBV DNA (often called ‘immune tolerant phase’). Over time,

immune recognition of HBV proteins expressed on hepatocytes leads to active hepatitis (HBeAg-positive hepatitis phase). Continued immune maturation often results in control (but not elimination) of the virus, as indicated by loss of HBeAg and acquisition of anti-HBe antibody (inactive carrier phase). Not all HBeAg-negative patients have inactive disease since some manifest abnormal liver enzymes and high levels of HBV DNA. This is thought to be a result of immune escape as a result of certain mutations of the virus (‘pre-core’).

Epidemiology of HBV-Associated Nephropathy

The reported prevalence of HBV-associated nephropathy, particularly MN, closely parallels the geographic patterns of prevalence of HBV (table 2). In children with HBV-associated nephropathy, it would appear that horizontal transmission of HBV is the predominant mode of transmission in most regions [25]. The rarity of HBV-associated nephropathy in developed countries such as the USA and Europe probably reflects the rarity of HBV infection, particularly in children. In the USA, HBV-related MN is most frequently seen in African-Americans [26]. In developed countries, HBV-associated nephropathy is frequently seen in adults who are high-risk groups such as intravenous drug abusers and in dialysis patients [24]. Introduction of HBV immunization in several endemic regions for HBV infection was one of the principle factors in lowering the incidence of HBV-associated nephropathy [24].

Another condition that has also been affected by HBV immunization is classic polyarteritis nodosa (PAN). Hepatitis B-associated PAN is a typical form of PAN whose pathogenesis has been attributed to immune complex deposition with antigen excess [27]. By concept, PAN is characterized by arteritis in medium-sized and small arteries without involvement of smaller vessels (e.g. without glomerulonephritis) [28]. PAN also differs from other vasculitis involving the kidney (e.g. Wegener and microscopic polyangiitis) in that antineutrophil cytoplasmic antibodies (ANCA) are not detected, relapses are rare, never occur once viral replication has been stopped and/or seroconversion occurs. Importantly, the frequency of hepatitis B-associated PAN has decreased due to widespread HBV immunization [27].

Clinical Course and Prognosis

The natural history of HBV-associated MN is not well defined. In children, HBV-associated MN has a favorable

Table 2. Worldwide distribution of HBV infection [24]

	Endemic status		
	low	intermediate	high
Prevalence			
Chronic infection	<2%	2–7%	8–15%
Total infection	<20%	20–60%	>60%
Distribution	North America	Eastern Europe	Southeast Asia
	Western Europe	Southern Europe	China
	Australia	Soviet Union	Philippines?
	New Zealand	Central Asia	Indonesia
	South America (Southern)	Japan	Middle East
		Israel	Africa
		South America (Northern)	Amazon Basin
			Pacific Islands
			Arctic (Inuit)

prognosis with high spontaneous remission rate, although some patients may remain proteinuric for 12 months or longer [18, 29–33]. In adults, however, HBV-associated MN is usually progressive with resolution of proteinuria being relatively uncommon [18, 29, 31, 34, 35]. Patients with nephrotic syndrome and abnormal liver function tests have an even worse prognosis with >50% progressing to ESRD in the short term [36]. Development of anti-HBeAg antibodies and HBeAg clearance are associated with remission of proteinuria [14, 30]. On the other hand, patients who do not clear the virus usually develop progressive renal failure [18, 29, 37].

Treatment

Antiviral Therapy

In the US, 7 agents have been approved by FDA for use in the treatment of adults with HBV. They all decrease HBV DNA levels. These agents are interferon- α (conventional interferon- α_2b and longer-acting peginterferon- α_2a), or nucleoside/nucleotide analogues (lamivudine, adefovir, entecavir, tenofovir, and telbivudine). Emtricitabine is available in Europe (in the US it is approved for HIV only).

The efficacy of these drugs has been assessed in RCT at 1 year (2 years with telbivudine and tenofovir). Longer-term follow-up (up to 5 years) is available for lamivudine, adefovir, entecavir, telbivudine and tenofovir in patient subgroups [1]. Treatment of patients with HBV infection and glomerulonephritis should be conducted using a multidisciplinary approach according to standard clinical

practice guidelines for HBV infection [1, 2], and with the understanding that the bulk of the available data regarding the use of anti-viral agents pertains to patients with HBV infection but not necessarily with renal involvement.

Antiviral agents may be used as monotherapy or in combination. Interferon use has a defined, self-limited course; in contrast, therapy with nucleoside or nucleotide analogues can be used long-term [2]. As it will be discussed shortly, each category of treatment has unique advantages and risks associated with administration of the drug. Health care providers should discuss with the patients the risks and benefits of the different treatment options in order to arrive at the best possible decisions.

A number of randomized control trials in both HBeAg-positive and -negative patients have shown that either monotherapy with pegylated-IFN or in combination with lamivudine is more effective than lamivudine alone at reducing HBV DNA, and in HBeAg-positive patients, inducing HBeAg seroconversion [38, 39]. Combined therapy, however, was not better than pegylated-IFN monotherapy in achieving suppression of HBV off therapy [38, 39]. Patients with kidney disease (serum creatinine >1.5 mg/dl) were excluded from these studies. There is only one study on the use IFN- α in 40 Chinese children with HBV-mediated MN who showed no response to corticosteroid treatment [40]. Twenty patients were randomized to IFN- α (group 1) three times a week for 12 months, and 20 to supportive treatment only (group 2) [40]. HBeAg and HBsAg were positive in all patients. At the end of the 3rd month of treatment, all patients in group 1 were free of proteinuria. In contrast, 10 patients (50%) in

Table 3. Dosage adjustment of drugs for hepatitis B according to kidney function

	CrCl >50 ml/min	CrCl 30–<50 ml/min	CrCl 10–<30 ml/min	CrCl <10 ml/min
Lamivudine	100 mg p.o. q.d.	100 mg first dose then 50 mg p.o. q.d.	100 mg first dose then 25 mg p.o. q.d.	35 mg first dose then 15 mg p.o. q.d. ^a
Adefovir	10 mg p.o. q.d.	10 mg p.o. every 48 h	10 mg p.o. every 72 h	no dosing recommended
Entecavir	0.5 mg p.o. q.d.	0.25 mg p.o. q.d.	0.15 mg p.o. q.d.	0.05 mg p.o. q.d.
Entecavir in lamivudine-refractory patients	1 mg p.o. q.d.	0.5 mg p.o. q.d.	0.3 mg p.o. q.d.	0.1 mg p.o. q.d.
Telbivudine	600 mg p.o. q.d.	600 mg p.o. every 48 h	600 mg p.o. every 72 h	600 mg p.o. every 96 h
Tenofovir	300 mg p.o. q.d.	300 mg p.o. q.d every 48 h	300 mg p.o. q.d every 72–96 h	300 mg p.o. once a week

^a Lamivudine should be dosed at 35 mg initially and then 10 mg daily for patients with CrCl <15 ml/min. Modified from Lau et al. [38] and Olsen and Brown [42].

group 2 had persistent heavy proteinuria. At the end of the 12th month, 8 patients (40%) in group 2 still had persistent heavy proteinuria and 12 patients (60%) had frequent relapses. The fact that children tend to improve regardless of treatment raises questions on the true efficacy of the therapy. On the other hand, 8 patients (40%) in group 1 underwent HBeAg seroconversion between the 4th and 6th months and HBsAg seroconversion between the 10th and 12th months. HBeAg– seroconversion (HBsAg+) occurred in 4 patients, while 4 patients had no change in HBV serological markers (HBeAg+/HBsAg+). The remaining 4 patients had HBeAg–/HBeAb+ HBsAg–/HBsAb– at the end of the 12th month. In contrast, none of the patients treated conservatively underwent seroconversion. On the other hand, in the only study to report on the effect of interferon- α_2b in 24 African children with HBV-associated MN, 10 of the children who completed 16 weeks of therapy (52.6%) responded with clearance of HBeAg by 40 weeks [41]. None cleared HBsAg. Remission of proteinuria occurred in all responders, with >90% of the patients either maintaining normal renal function or showing renal function improvement. HBV DNA levels decreased in this group. None of the 9 patients who did not clear HBeAg showed remission of proteinuria, while 2 developed progressive renal failure. In the control group, only 5% of the patients showed spontaneous clearance of HBeAg, and none had remission of proteinuria [41]. These studies support the notion that antiviral therapy is effective in inducing proteinuria remission and preserving renal function in patients with HBV-associated MN.

An advantage of IFN- α is that it is given for a defined course (16–48 weeks), but requires subcutaneous injection and is associated with a number of side effects including influenza-like symptoms, hematologic abnormalities, depression, anorexia, diarrhea, dermatitis, alopecia, and increased infection rate. Treatment with IFN- α (conventional or pegylated) has the advantage of the absence of resistance as well as the potential for immune-mediated containment of HBV infection with an opportunity to obtain a long-term suppression of HBV off-treatment and a chance of HBsAg loss in a small number of patients who achieve and maintain undetectable HBV DNA. IFN- α is, however, contraindicated in patients with decompensated liver disease.

Nucleoside and nucleotide analogues are administered orally, are associated with more profound HBV DNA suppression than IFN- α , and may be safely used in previous nonresponders to IFN- α therapy. Unfortunately, resurgence of HBV DNA levels occurs if the drug is prematurely discontinued or if resistance to the drug develops. All nucleoside and nucleotide analogues need dose adjustment in patients with kidney insufficiency (see table 3).

Data on lamivudine use in patients with kidney disease are limited to uncontrolled studies on small numbers of patients. It is administered once daily, typically at a dose of 100 mg, and is generally well tolerated and safe in long-term studies. Side effects, when they occur, are generally mild and include headache, nausea, and vomiting [42]. Tang et al. [43] treated 10 HBsAg-positive patients with biopsy-proven MN, elevated liver enzymes,

and HBV DNA with lamivudine for 12 months (group 1), and compared their clinical course with a historical control group of 12 patients with HBV infection, elevated liver enzymes, and MN who had been followed in the pre-lamivudine era (group 2). At 6 months, lamivudine treatment was associated with significant reduction in proteinuria, increase in serum albumin, normalization of liver enzymes, and disappearance of circulating HBV DNA during the first year. Four (40%) and 6 (60%) patients went into complete remission of proteinuria (<0.3 g/day) at 6 and 12 months, respectively. In group 2, significant proteinuria persisted during the first year. One (8.3%) and 3 (25%) patients went into remission. Cumulative 3-year renal survival (using ESRD as primary end point) was 100% in group 1 and 58% in group 2 ($p = 0.024$). Lamivudine was well tolerated and not associated with any adverse events [43]. However, lamivudine dose needs to be adjusted according to the degree of kidney function [44]. More recently, Chuang et al. [45], reported on the case of a 22-year-old male with HBV, MN and nephrotic syndrome who had complete remission after lamivudine monotherapy. The significance of these data resides in the proof of the concept that HBV suppression by antiviral drugs leads to improved renal outcome, not necessarily that lamivudine is to be used in these patients. This is because lamivudine has a big disadvantage of being susceptible to resistant mutations. Due to the high incidence of resistance (14–20% at 1 year and as high as 69% at 5 years), which essentially decreases the effectiveness of the drug, current guidelines recommendations consider lamivudine as a second agent. An additional factor when using lamivudine is the development of cross-resistance with other nucleoside analogues (i.e. telbivudine and entecavir) [46].

Adefovir dipivoxil is a phosphonate nucleotide analog of adenosine, which competitively binds HBV DNA polymerase and serves as a chain terminator. Adefovir is used at a dose of 10 mg daily and has been effective in the treatment of naive HBeAg-positive and -negative patients, lamivudine-resistant patients, patients coinfecting with HIV, and in the postliver transplant setting [47–50]. Unfortunately, the inhibitory effect of adefovir in HBV viral replication is relatively weak and viral rebound occurs soon after treatment is stopped [51]. In addition, the development of resistance is increasingly recognized in patients treated with adefovir monotherapy long term [51]. Furthermore, the use of adefovir in patients with kidney disease has been limited by concern for potential nephrotoxicity. In animal studies, renal toxicity is characterized by tubular nephropathy and increase in serum creati-

nine. These changes developed, however, at doses 3–8 times greater than the recommended dose for humans. Although patients with significant renal disease were excluded from the studies cited above, significant increases in creatinine were not seen on adefovir therapy at the dose of 10 mg a day [52]. In addition, adefovir has been studied in 11 patients with lamivudine-resistant HBV status after kidney transplant, and found to be both safe and efficacious in this patient population [53]. The current guideline also relegates adefovir as a second tier drug because of its weak potency and potential concern for renal toxicity in comparison to newer agents such as tenofovir or entecavir.

Similarly, telbivudine is a potent antiviral drug that has been shown to be effective in suppressing HBV in both HBeAg-positive and -negative patients. Unfortunately, it is more prone to the development of resistant mutations than entecavir or tenofovir. It also has toxicity including myopathy and, when combined with interferon, peripheral neuropathy.

On the other hand, entecavir is a guanosine analog that inhibits HBV DNA polymerase at both the priming and elongating steps of DNA synthesis. It has been shown to be more effective than lamivudine in suppressing viral replication, in both HBeAg-positive and -negative patients [54]. Recent data of HBeAg-positive patients treated with 0.5 mg of entecavir showed better histologic improvement than those on lamivudine (72 vs. 62%) as well as higher clearance of HBV DNA levels (69 vs. 38% in the lamivudine group). HBeAg seroconversion rates, however, of 21% with entecavir and 18% with lamivudine were not significantly different [55]. Similar results have been obtained in HBeAg-negative patients treated with entecavir versus patients on lamivudine [56]. Resistance to entecavir is rare, but was seen in over 7% of the lamivudine-resistant patients treated with entecavir for 1 year, making it unlikely to be the drug of choice as a monotherapy in this situation. Entecavir appears to be safe in patients with kidney diseases but the dose needs to be adjusted in patients with impaired kidney function (see table 3).

In 2 recent randomized control trials, tenofovir has been shown superior to adefovir. In patients HBeAg positive, 48 weeks' treatment with tenofovir resulted in significantly higher proportions of patients with undetectable HBV DNA by PCR (76 vs. 13%), normalization of liver enzymes (68 vs. 54%), HBsAg loss (3 vs. 0%) and HBeAg seroconversion (21 vs. 18%) compared to treatment with adefovir [57]. In HBeAg-negative patients, 48-week-long treatment with tenofovir resulted in a sig-

nificantly higher proportion of patients with undetectable HBV DNA (93 vs. 63%) than adefovir and similar proportion of patients achieving liver enzymes normalization (76 vs. 77%), or histologic response (72 vs. 69%) [57]. Tenofovir resistance was not detected in any of the patients up to 96 weeks of treatment, but additional therapy with emtricitabine was given to some patients who remained viremic at week 72. Tenofovir has been reported to cause Fanconi syndrome and kidney failure [58]. Despite the robust potency and resistance profile of tenofovir, some experts recommend avoiding tenofovir in patients with HBV-related renal involvement because of the potential for renal toxicity.

As stated before, the benefit of antiviral therapy in patients with HBV-mediated glomerular disease was demonstrated only with lamivudine so far. However, it is likely that HBV suppression via other, more modern agents such as entecavir and tenofovir, will benefit those patients as well. Nonetheless, well-designed and well-conducted randomized controlled trials are sorely needed to conclusively demonstrate a beneficial effect on renal outcomes in patients with HBV-mediated kidney disease undergoing antiviral therapy.

Immunosuppressive Therapy in HBV-Associated Nephropathies

Corticosteroids

Corticosteroid therapy has been used in some patients with HBV-associated nephropathy as a therapeutic trial for symptomatic relief of proteinuria. Lai et al. [59] investigated the therapeutic benefits and risks of a 6-month course of corticosteroid in 8 patients with MN, positive HBsAg, high titers of anti-HBcAg (HBeAg positive in 4 patients) and normal liver enzymes. Nephrotic syndrome was present in 7 patients. The use of corticosteroid resulted in remission of the nephrotic syndrome in 3 patients, but proteinuria persisted in 5 patients. Transient liver impairment was observed in 3 patients. As result of the use of corticosteroid therapy, transient viral replication with increased serum concentration of HBeAg and HBV DNA were observed. Similar increase in viral replication was reported by Cadrobbi et al. [60] in a 3-year-old boy with chronic active HBV and MN treated with corticosteroids. Withdrawal of corticosteroid therapy resulted in resolution of HBV replication, while both glomerulonephritis and chronic hepatitis went into remission. In at least one patient with HBV and MN where renal biopsies were taken before and after corticosteroid therapy, this

form of therapy was associated with progression of glomerulosclerosis on light microscopy, while electron microscopy showed virus-like particles (40–50 nm in diameter) in the glomeruli only in the biopsy performed after corticosteroid therapy [61]. In this patient, corticosteroid therapy was associated with an increase in liver enzymes, as well as serum levels of HBeAg, and HBV DNA, suggesting active viral replication. In one case of a patient with HBV-associated MN withdrawal of immunosuppressive treatment resulted in progression to a crescentic glomerulonephritis [62]. The authors speculate that immunosuppressive therapy stimulated HBV replication, and withdrawal of immunosuppression led to a return of the patient's immune competence with the resulting development of a crescentic glomerulonephritis. The available evidence does not support use of corticosteroids in HBV-associated MN; corticosteroids may in fact enhance viral replication and precipitate hepatic flares [36].

Other Immunosuppressive Agents

A beneficial effect of plasma exchange used in combination with antiviral agents and/or immunosuppressant agents has been reported in patients with HBV-associated PAN [63, 64]. Another agent that has been increasingly used in patients with autoimmune diseases including MN and ANCA-associated vasculitis is rituximab, a monoclonal antibody against the CD20 antigen present on B cells and approved by the FDA in 1997 for the treatment of relapsed or refractory non-Hodgkin's lymphoma and more recently for patients with rheumatoid arthritis [65, 66]. However, a word of caution should be said about rituximab, since in patients with HBV, the use of rituximab has resulted in HBV viral reactivation, the severity of which has resulted in death in some patients [67–70]. Preemptive use of entecavir has enabled successful management of HBV reactivation, although mild to moderate hepatic flare can still occur [71]. Similarly, the use of cytotoxic agents [72] and of azathioprine and cyclosporine in patients undergoing transplantation (even in HBsAg-negative patients with past HBV infection) has resulted in reactivation of HBV and fatal acute hepatitis in some cases [73, 74].

Conclusions

In the past decade, the advance in anti-HBV therapy has revolutionized management of patients with this infection. In addition to registration trials that are mentioned in this review, a randomized trial has shown that

anti-HBV therapy alters the 'hard' endpoints, such as progression of cirrhosis and development of hepatocellular carcinoma [75]. Nonetheless, there remain limitations to the current therapy: the realistic goal of HBV therapy remains suppression of the virus rather than eradication, thus requiring long-term therapy. This is associated with concerns about financial burden, patient adherence and resistant mutations as well as potential for toxicity when the HBV drugs are used long term.

Obviously, HBV infection does not uniformly lead to development of renal disease. Incidence, risk factors and the natural history of renal involvement among patients with HBV infection are poorly understood [42]. Cases of spontaneous remission and of remission associated with HBeAg seroconversion have been described (especially in younger patients). The heterogeneity of patients with HBV infection (e.g. degree of liver compromise, renal involvement, degree of renal insufficiency) illustrates the complexity in establishing treatment guidelines in these patients, including those with HBV-mediated kidney disease.

In our opinion, evidence to date suggests that antiviral therapy improves HBV-associated MN. However, this conclusion is based on a paucity of available information

and greatly inferred from results of treatment of HBV patients in general. Thus, there is a need for good quality prospective controlled studies to address the effects of these interventions in patients with HBV-associated glomerular diseases, particularly in children, so we can better define the most effective therapies for these patients. Similarly, antiviral therapy should be considered in patients with renal insufficiency, but its overall long-term effect in changing the outcome of HBV infection in these patients remains to be proven.

The choice of the specific agent (e.g. interferon vs. an oral antiviral) is dictated by the overall clinical picture and best conducted via a multidisciplinary approach. However, in patients with HBeAg-negative disease, a long-term oral nucleoside analogue such as entecavir or tenofovir would be reasonable. Attractive candidates for interferon treatment include young patients, HBeAg positive and with elevated liver enzymes. Naturally, the dosing of these antiviral agents must be adjusted to the degree of kidney function. Finally, immunization and appropriate screening programs are extremely important steps in the effort to eradicate HBV infections and reduce the incidence of HBV-associated kidney diseases.

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Editorial Comment

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The review of Elewa and colleagues highlights issues related to the association between HBV infection and nephropathies. This includes the possible fortuitous association between chronic HBV infections in endemic areas and the new onset of a nephropathy, as well as coinfections with other viruses such as HCV and HIV. The review informs the reader of the scope of antiviral therapies currently available to treat HBV including interferon- α , nucleoside/nucleotide analogues (lamivudine, adefovir,

entecavir, tenofovir, and telbivudine) and emtricitabine. The authors note that the beneficial effect of antiviral therapy in patients with HBV-mediated glomerulonephritis has so far only been demonstrated with lamivudine. Of note, most published treatment data range from anecdotal reports to small and poorly controlled studies, hence the call for well-designed randomized controlled trials of antiviral therapy in patients with HBV-associated nephropathies.