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Treatment of Hepatitis B Virus-Associated Membranous Nephropathy: Lamivudine Era versus Post-Lamivudine Era

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The prevalence of hepatitis B in Korea is 3% to 4%, which is lower than that in Southeast Asia, China, or Africa (8% to 15%). However, the prevalence in Korea is higher than in North America or Western Europe (< 2%) [1]. The majority of patients with hepatitis B in Korea have genotype-C virus (HBV), which exhibits a slower rate of hepatitis B e antigen (HBeAg) seroconversion, rapid progression to liver cirrhosis and hepatocellular carcinoma, reduced interferon (IFN) treatment effect, and higher HBV DNA reactivation rate after antiviral treatment.

The higher prevalence of chronic hepatitis B in Korea could be a serious problem in kidney transplantation because patients may acquire the virus after transplantation. However, the data from the Organ Procurement Transplant Network/United Network for Organ Sharing revealed no difference in 5-year-graft survival between hepatitis B surface antigen (HBsAg)(+) and HBsAg (-) recipients in 1995. This phenomenon can be attributed to the fact that a reduction in viral load occurred secondary to the use of lamivudine in 1996 and entecavir and adefovir in 2000, resulting in improved graft survival. However, because the incidence of hepatic failure is statistically higher in HBsAg (+) recipients, extra attention should be given to these patients' long-term survival after transplantation.

Hepatitis B associated with glomerulonephritis includes membranous nephropathy (MN), membranoproliferative glomerulonephritis, polyarteritis nodosa, essential mixed cryoglobulinemia, IgA nephropathy, and focal segmental glomerulonephritis. MN is the most common renal manifestation of hepatitis B and usually develops in the chronic hepatitis state. The universal HBV vaccination program recently reduced the HBV carriage rate and decreased hepatocellular carcinoma in children. It also significantly reduced the incidence of hepatitis B-associated MN in children in the two decades since the introduction of the universal HBV vaccination program in Taiwan [2].

The pathogenesis of HBV-associated MN is considered to involve deposition of hepatitis Ag and Ab immune complexes in the subepithelial space. This hypothesis is based on the presence of HBV in kidney tissue, mainly the glomerular area. There is much more direct evidence of an association between hepatitis B-associated MN and HBV than of the association of other types of HBV with glomerulonephritis. By immunofluorescence, HBeAg is predominantly observed; however, hepatitis B core antigen or HBsAg may also be present. Virus-like particles are predominantly observed in subepithelial and subendothelial electron-dense deposits by electron microscopy.

The most common clinical features are proteinuria and edema. HBV-associated MN serology reveals the presence of HBsAg and anti- hepatitis B core antibody in most pa-

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tients. Seroconversion of HBeAg to HBeAb is related to recovery of nephrotic syndrome. Low levels of complement C3 and C4 (15% to 64%) may be observed, and circulating immune complexes are frequently detected.

Although the natural history of the disease often involves remission with preservation of renal function, adults with HBV-MN, unlike affected children, typically develop disease progression; spontaneous complete remission of nephrotic syndrome with seroconversion to anti-HBe is uncommon [3]. The relatively poor clinical outcomes in adults with HBV-MN have led to various therapeutic approaches including corticosteroids, thymic extracts, acyclovir, IFN, and lamivudine.

Among the various kinds of HBV-associated glomerulonephritis, hepatitis B-associated MN shows a clinical manifestation relevant to circulating HBeAg and characteristic deposition of HBV DNA in renal tissue, conferring the rationale for anti-viral treatment. In practice, antiviral therapy has been recommended by many studies of hepatitis B-associated glomerulonephritis because it can effectively inhibit HBV replication and attenuate proteinuria. Because previous studies showed that lamivudine therapy is significantly associated with a better outcome than IFN therapy [4,5], the anti-viral drug lamivudine has been recommended as the most important therapy for hepatitis B-associated MN. However, lamivudine-resistant HBV mutation could decrease the efficacy of anti-viral therapy. The incidence of lamivudine-resistant HBV strains is up to 20% per year. Recurrence of proteinuria after cessation of lamivudine may be another issue.

Unfortunately, there have been no controlled trials of treatments for hepatitis B-associated MN with lamivudine-resistant strains despite the increasing frequency of lamivudine-resistant HBV mutant strains. Sun et al. [6] reported their clinical experience of addition of adefovir to lamivudine and substitution of clevudine for lamivudine for hepatitis B-associated MN with lamivudine-resistant strains. They also reported the clinical effects of entecavir in HBV-related MN, showing HBeAg seroconversion, HBV clearance, and subsequent complete remission of proteinuria. This paper is notable because new drugs such as entecavir, adefovir, and clevudine have been introduced to treat chronic hepatitis B, but there are no clinical data regarding their efficacy in treating HBV-MN.

Although the effect of entecavir for hepatitis B-associated MN or other HBV-associated glomerulonephritis has not been proven in a controlled trial, nephrologists could consider it a first-line therapy for treatment of hepatitis B-associated MN because it is currently the first-line agent for treatment of chronic active hepatitis B due to its strong HBV suppressive effect and low rate of resistance [7]. However, for patients with hepatitis B-associated MN with lamivudine-resistant strains, the effects of these new drugs on remission of proteinuria and renal outcomes should be evaluated in controlled clinical trials.

Use of all of the aforementioned antiviral agents should be adjusted based on renal function. In particular, adefovir is known to be nephrotoxic and was recently reported to be associated with the development of secondary MN in a liver transplantation patient [8]. Table 1 shows the antiviral agent dose recommendations for patients with impaired renal function.

As antiviral treatment for chronic hepatitis B has become more common, the need for use of immunosuppressive agents has almost disappeared. As a result of the use of corticosteroid therapy, transient viral replication with increased serum concentrations of HBeAg and HBV DNA were observed [9]. Combination therapy with lamivudine and corticosteroids resulted in a rapid reduction of proteinuria and frequent HBV DNA reactivation after treatment compared with lamivudine-only treatment [10]. Similarly, the use of cytotoxic agents in conjunction with azathioprine and cyclosporine in some cases resulted in reactivation of HBV and fatal acute hepatitis. Rituximab has been increasingly used in patients with idiopathic MN; however, there are no case reports of application of treatment for HBV-associated MN. The current clinical role of immunosuppressive agents in the treatment of HBV-associated MN is small, but their roles in conjunction with antiviral agents for uncontrolled diseases should be reevaluated in the coming post-lamivudine era.

Secondary MN is the most common renal manifestation of chronic HBV infection. Clinical manifestations are relevant to circulating HBeAg and intraglomerular deposition of viral DNA, and the introduction of lamivudin has led to improved renal outcome without serious side effects. However, the clinical limitation of prolonged treatment with lamivudine is the emergence of drug-resistant strains. Unfortunately, although new antiviral agents for HBV have been introduced in clinical practice, there have been no controlled trials of treatments for hepatitis B-associated MN in the post-lamivudine era. Effects of these new drugs on the remission of proteinuria and renal outcomes should be evaluated in controlled clinical trials. The possible role

Table 1. Recommended dosing of antiviral agents in adults with kidney diseases

		Ccr, mL/min	Reference dose
Lamivudine		≥ 50	100 mg p.o. q.d.
		30–49	100 mg first dose, then 50 mg p.o. q.d.
		15–29	35 mg first dose, then 25 mg p.o. q.d.
		5–14	35 mg first dose, then 15 mg p.o. q.d.
		< 5	35 mg first dose, then 10 mg p.o. q.d.
Adefovir		≥ 50	10 mg p.o. q.d.
		20–49	10 mg p.o. every 48 hr
		10–29	10 mg p.o. every 72 hr
		< 10, hemodialysis	10 mg p.o. every wk
Entecavir	Initial therapy	≥ 50	0.5 mg p.o. q.d.
		20–49	0.25 mg p.o. q.d.
		10–29	0.15 mg p.o. q.d.
		<10, hemodialysis	0.05 mg p.o. q.d.
	Lamivudine refractory	≥ 50	1.0 mg p.o. q.d.
		20–49	0.5 mg p.o. q.d.
		10–29	0.3 mg p.o. q.d.
		<10, hemodialysis	0.1 mg p.o. q.d.
Telbivudine		≥ 50	600 mg p.o. q.d.
		20–49	600 mg p.o. every 48 hr
		< 30 (pre-dialysis)	600 mg p.o. every 72 hr
		Hemodialysis	After dialysis, 600 mg p.o. q.d.

Ccr, creatinine clearance; p.o. q.d., by mouth every day.

of immunosuppressive agents should be reevaluated in terms of intractable cases in the coming post-lamivudine era.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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