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ORIGINAL ARTICLE

Short-Term Corticosteroids Then Lamivudine and Plasma Exchanges to Treat Hepatitis B Virus–Related Polyarteritis Nodosa

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Objective. **To assess the efficacy and safety of lamivudine, an antiviral agent that strongly inhibits hepatitis B virus (HBV) DNA replication, combined with plasma exchanges after short-term corticosteroids for HBV-related polyartertitis nodosa (PAN).**

Methods. **Ten patients (8 men, 2 women, mean ± SD age 50.4 ± 14.4 years) with previously untreated HBV-related PAN were included in a multicenter, prospective, observational trial. Oral prednisone (1 mg/kg/day) was given for 1 week, then tapered and withdrawn within 1 week. Then, lamivudine (100 mg/day or less in the case of renal insufficiency) was started for a maximum of 6 months. Plasma exchanges were performed simultaneously and scheduled as follows: 3/week for 3 weeks, 2/week for 2 weeks, then 1/week until hepatitis B e antigen (HBeAg) to anti-HBe antibody (HBeAb) seroconversion was obtained or until 2–3 months of clinical recovery was sustained. The primary trial endpoint was clinical recovery from HBV-PAN at 6 months. The secondary endpoint was loss of detectable serum HBeAg and HBV DNA, and HBeAg to HBeAb seroconversion at 9 months.**

Results. **One death, attributed to catheter-related septicemia, was recorded. At 6 months, all 9 survivors had achieved clinical recovery and by 9 months, 6 of 9 (66%) had seroconverted.**

Conclusion. **The strategy of short-term steroids followed by lamivudine and plasma exchanges effectively led to recovery from HBV-PAN. Because of its oral administration and good safety profile, lamivudine should henceforth be considered the antiviral agent of choice to treat HBV-related PAN.**

KEY WORDS. Polyarteritis nodosa; Hepatitis B virus; Corticosteroids; Plasma exchanges; Lamivudine.

INTRODUCTION

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis affecting medium-sized arteries (1). Although its etiology remains elusive, the strong association between PAN and hepatitis B virus (HBV) infection (2–4) clearly suggested a causal link with this agent in many patients. Epidemiologic data suggest that the frequency of HBV-related PAN (HBV-PAN) might currently be declining in developed countries (5), most probably as a consequence of effective vaccination programs and mandatory screening of blood donors.

Conventional therapy of PAN relies on corticosteroids and, for severe cases, adjunctive cyclophosphamide. Although this regimen may also control HBV-PAN (3), prolonged use of corticosteroids (6,7) or cytotoxic agents (8,9)

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in HBV-infected patients raises some concern with regard to their stimulatory effect on virus replication and enhanced host immune response against the virus that may cause fulminant liver disease. Therefore, 15 years ago, our group devised an original therapeutic strategy based on short-term corticosteroids, followed by the combination of plasma exchanges and an antiviral agent that successfully treated HBV-PAN (10,11). Since then, various antiviral agents, e.g., vidarabine (12) and interferon-2α (13), have had proven efficacy in this setting.

Lamivudine (also known as 3TC) is a nucleoside analog that potently inhibits HBV DNA replication. It has been approved as the treatment of choice for chronic HBV infection (14–16) and also has shown efficacy against acute HBV infection (17–19). The present trial was established to investigate the efficacy and tolerance of lamivudine combined with plasma exchange after short-term corticosteroids prescribed to 10 consecutive untreated patients with recent-onset HBV-PAN.

PATIENTS AND METHODS

Patients. This multicenter, prospective, observational therapeutic trial included 10 consecutive patients with newly diagnosed and previously untreated HBV-PAN. To be eligible, patients had to be at least 18 years old and PAN had to fulfill the American College of Rheumatology (ACR) criteria (20); histologic proof of vasculitis was preferred but not required. Patients also had to have detectable hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and detectable levels of serum HBV DNA determined using a hybridization assay or polymerase chain reaction (PCR). Abdominal angiography was recommended for patients with persistent abdominal pain. To avoid the risk of hemorrhage associated with the puncture of potentially present arterial hepatic microaneurysms, liver biopsy was not systematically required. Patients were excluded when any of the following were present: coinfection with hepatitis C virus (HCV) or human immunodeficiency virus (HIV); positive antineutrophil cytoplasm antibodies (ANCA); pancreatitis (because of its potential aggravation under lamivudine therapy); pregnancy or breastfeeding; absence of contraception for women of childbearing age.

All the patients underwent an in-depth investigation of their disease at study enrollment. Poor general condition included weight loss, defined as a loss of >5% of the usual body weight during 1 month, asthenia, or temperature >38°C without concurrent infection. Virologic investigations comprised complete screening for HBV markers (HBsAg, anti-HBc antibodies [Ab], HBeAg, anti-HBeAb, serum DNA], serologic screening for HCV and, when positive, PCR, and HIV serology. ANCA were sought by immunofluorescence and anti-proteinase 3 and anti-myeloperoxidase activities were systematically determined using an enzyme-linked immunosorbent assay. Disease severity was assessed with the five-factors score (FFS) (21). The FFS is defined by the following parameters: proteinuria > 1 gm/day, renal insufficiency (creatininemia > 1.58 mg/dl), cardiomyopathy, gastrointestinal manifestations, and central nervous system involvement. FFS was previously shown to have significant prognostic value with 5-year survival rates of 88% when FFS = 0, 74% when FFS = 1, and 54% when FFS ≥ 2 (21).

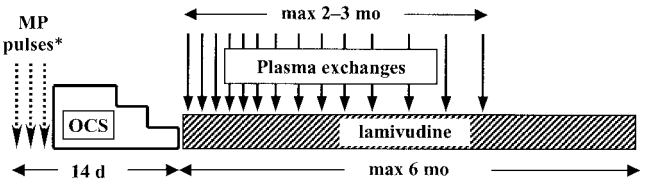

Figure 1. Therapeutic scheme for hepatitis B virus-related polyarteritis nodosa. Plasma exchanges and lamivudine could be prescribed for no more than 2–3 months and 6 months, respectively. They were stopped as soon as HBe seroconversion was documented. MP = methylprednisolone; OCS = oral corticosteroids; * = optional.

Treatment. The therapeutic scheme used for the 10 patients is shown in Figure 1. Treatment was started with prednisone (1 mg/kg/day) for 1 week; for severely ill patients, corticosteroid therapy could be initiated by a methylprednisolone pulse (15 mg/kg) for 1–3 days. The prednisone dose was rapidly tapered by half every day until complete withdrawal by the end of week 2. Then, lamivudine and plasma exchanges were begun. Patients took 100 mg of oral lamivudine once a day; for patients with impaired renal function, the lamivudine dosage was adjusted to reflect creatinine clearance as calculated with the Cockcroft and Gault formula (Table 1) (22). Lamivudine was maintained for 6 months or stopped at the time of seroconversion to anti-HBsAb. Plasma exchange sessions were scheduled as follows: 3/week for 3 weeks, 2/week for 2 weeks, then 1/week for the following weeks; they were stopped at the time of HBeAg to HBeAb seroconversion (see below) or after stable clinical recovery had been obtained and maintained for ~2–3 months. For each plasma exchange session, the circuit was primed with 1 liter of starch and 60 ml of plasma/kg were replaced with 4% albumin. Lamivudine was taken after each plasma exchange session to avoid drug removal during the procedure.

Outcome measures. During 6 months of treatment and through months 9 of the trial, the main clinical and laboratory parameters of all the patients were closely monitored. Patients' outcomes were assessed with respect to response to therapy, relapses, and mortality. The primary trial endpoint was clinical recovery from PAN at 6 months,

Table 1. Lamivudine dose adaptation as a function of creatinine clearance (CrCl)

CrCl (ml/min)	Daily dose (mg)	
	Day 1	Thereafter
≥50	100	100
30–49	100	50
15–29	100	25
5–14	35	15
<5	35	10

Table 2. Demographics and principal clinical manifestations in 10 patients with HBV-related PAN*

Parameter	Value
Age, mean ± SD (range) years	50.4 ± 14.4 (29–67)
M/F	8/2
Poor general condition	9 (90)
Weight loss, >5% body weight	9 (90)
Fever >38°C	7 (70)
Myalgias/arthralgias	8 (80)
Mononeuritis multiplex	9 (90)
Superficial peroneal nerve, no.	7
Deep peroneal nerve, no.	3
Cubital nerve, no.	3
Bilateral involvement, no.	4
Gastrointestinal tract involvement	5 (50)
Cutaneous involvement	2 (20)
Vascular nephropathy	3 (30)
Proteinuria >1 gm/day	3 (30)
Hematuria	1 (10)
Creatininemia, mean ± SD (range) mg/dl	1.65 ± 1.96 (0.67–7.14)
Renal insufficiency†	2 (20)
Orchitis, no./n (%)	5/8 (63)
Hypertension	3 (30)
Cardiomyopathy	2 (20)
Central nervous system involvement	1 (10)

* Values are numbers (%) unless otherwise specified. HBV = hepatitis B virus; PAN = polyarteritis nodosa.
† Defined as creatininemia >1.58 mg/dl.

defined as no sign of active vasculitis, with either complete resolution or clear-cut stabilization of all signs of organ system disease activity. The secondary endpoint was the loss of detectable circulating levels of HBeAg and HBV DNA, and the appearance of anti-HBeAb (referred to as HBe seroconversion) at 9 months. Relapse was defined as the reappearance of clinical and/or laboratory signs of vasculitis.

Ethics. This trial was approved by the Comité Consultatif des Personnes Participant à la Recherche Biomédicale (CCPPRB; reference 102-98).

RESULTS

Patient characteristics. Ten HBV-PAN patients, 8 men and 2 women, mean ± SD age 50.4 ± 14.4 years, were included between January 1, 1999 and February 28, 2000. All the diagnoses met ≥3 of the 10 ACR criteria, with 4 items present in 3 patients, 5 items in 4 patients, 6 items in 1 patient, and 7 items in 1 patient. The patients' principal clinical manifestations and laboratory results at entry are summarized in Tables 2 and 3. Histologic proof of vasculitis was obtained in muscle, peripheral nerve, or skin biopsies for 7 patients. Three patients were intravenous drug abusers, who potentially contracted HBV infection through percutaneous exposure; for the remaining 7 patients, the route of HBV acquisition was unknown. Nine patients had anti-HBcAb of the IgM isotype, suggesting recent infection. Liver biopsy was performed in 3 patients and revealed active hepatitis with calculated histology activity index scores of 1, 1, and 10 (23). Microaneurysms or stenoses were observed in 1 of 3 patients who had abdominal angiograms. FFS were 5 for 1 patient, 2 for 2, 1 for 1, and 0 for the other 6.

Outcome results. At 6 months, 9 of 10 patients had achieved clinical recovery; the remaining patient died after an initial clinical response. None of the 9 survivors relapsed during the subsequent 3 months of followup. In a per-protocol analysis at 9 months, 6 (66%) of the 9 survivors had achieved HBe seroconversion with a mean ± SD treatment onset to seroconversion interval of 158 ± 85 days (range 13–252 days). HBsAg became undetectable in 3 of the 9 survivors concomitant with anti-HBsAb seroconversion. Among the 3 patients who had not seroconverted to anti-HBeAb, 2 had sustained suppression of serum HBV DNA to undetectable levels at several consecutive determinations. Alanine or aspartate aminotransferase were never elevated in any patient during therapy or after therapy withdrawal, particularly concurrently with the loss of markers of HBV replication. Treatment was well tolerated in 9 of 10 patients; the sole death was attributed to *Staphylococcus epidermidis* septicemia related to central catheter (inserted for plasma exchange) infection. Sequelae were end-stage renal failure in 1 patient requiring dialysis, and minor sensorimotor deficits following mononeuritis multiplex in 9 patients.

DISCUSSION

The results of this observational trial indicate that lamivudine combined with plasma exchange after short-term corticosteroids is an effective therapy for HBV-PAN. This strategy achieved clinical recovery in all 10 patients and a 66% HBe seroconversion rate, defined as suppression of serum HBeAg and HBV DNA to undetectable levels and the presence of anti-HBeAb. This seroconversion rate is higher than the 36% rate previously observed with vidarabine (12) and equal to that obtained with interferon-2α (13). Tolerance of this therapy was good, although 1 patient succumbed to septicemia that was attributed to *S. epidermidis* contamination of the central catheter used for plasma exchange. Therefore, we recommend that plasma exchange should be performed through a peripheral venous access, which is less susceptible to infectious complications.

The therapeutic modality used to treat HBV-PAN is specifically tailored to its pathogenesis (24). In this setting, corticosteroids are administered for only 2 weeks to rapidly contain the potentially life-threatening organ damage caused by the inflammatory phenomena of systemic vasculitis. The cornerstone of this protocol is based on the subsequent initiation of plasma exchange combined with an antiviral agent: plasma exchanges remove the immune

Table 3. Detailed clinical and biologic manifestations in 10 patients with HBV-related PAN*

Patient no/sex/age, years	Clinical symptoms	Angiography findings	Vasculitis-proven biopsy	Creatininemia (mg/dl)	FFS	AST/ALT	HBeAg seroconversion/time
1/M/55	Poor condition, high ESR, fever, weight loss, myalgias, arthralgias, Raynaud's phenomenon, abdominal pain, proteinuria, hypertension, mononeuritis multiplex	Microaneurysms	Neuromuscular	1.86	2	N/N	Yes/6 mo
2/M/67	Poor condition, high ESR, fever, weight loss, myalgias, arthralgias, mononeuritis multiplex		Neuromuscular	1.11	0	1.5N/2N	Yes/6 mo
3/M/37	Poor condition, high ESR, fever, weight loss, arthralgias, mononeuritis multiplex, orchitis			1.13	0	6N/6N	Yes/2 mo
4/M/70	Poor condition, high ESR, fever, weight loss, myalgias, arthralgias, purpura, abdominal pain, cholecystitis, proteinuria, hypertension, mononeuritis multiplex, orchitis	Normal	Skin	0.87	2	N/N	No (died)
5/M/50	Poor condition, high ESR, fever, weight loss, myalgias, arthralgias, abdominal pain, mononeuritis multiplex, orchitis		Neuromuscular	0.67	0	2N/2N	Yes/8 mo
6/F/61	Poor condition, high ESR, fever, weight loss, myalgias, arthralgias, abdominal pain, hypertension, mononeuritis multiplex		Neuromuscular	0.85	0	2N/2N	No
7/F/60	Poor condition, high ESR, fever, weight loss, myalgias, arthralgias, mononeuritis multiplex			1.13	0	N/N	Yes/0.5 mo
8/M/35	Poor condition, weight loss, myalgias, arthralgias, gangrene, abdominal pain, mononeuritis multiplex, orchitis, cardiomyopathy		Neuromuscular	1.35	1	N/1.5N	Yes/6 mo
9/M/29	Poor condition, weight loss, cardiomyopathy, abdominal pain, cholecystitis, proteinuria, hematuria, anuria, central nervous system involvement, orchitis	Microaneurysms		7.14	5	1.5N/1.5N	No
10/M/40	Myalgias, arthralgias, high ESR, mononeuritis multiplex		Muscular	0.7	0	1.5N/1.5N	No

* Poor general condition was defined as asthenia, loss >5% of usual body weight, and/or fever >38°C without concurrent infection. HBV = hepatitis B virus; PAN = polyarteritis nodosa; FFS = five-factors score; ALT/AST = serum alanine/aspartate aminotransferase; HBeAg = hepatitis B e antigen; ESR = erythrocyte sedimentation rate; N = normal; mo = months.

complexes, which are the major determinant of vessel inflammation (24), and the antiviral agent is added to facilitate immune-complex clearance by diminishing the virus load and, eventually, to stop virus replication. Although this approach has never been evaluated in a randomized trial, indirect evidence of its effectiveness has been provided by long-term followup data of our former trials showing a 0% relapse rate among patients achieving HBe sercoconversion and a 7-year overall survival rate of 83% (25).

Data from patients whose duration of HBV carrier status could be defined in previous observations indicated that PAN occurs early during the course of HBV infection, most frequently within the 12 months following contamination (25). Because the natural history of acute HBV infection is characterized by a spontaneous anti-HBsAb seroconverion rate of >90% of adult cases (26), recovery might occur spontaneously. However, in light of the potential life-threatening organ damage caused by uncontrolled vasculitis, it would be unethical to withhold treatment waiting for a hypothetical self resolution or to evaluate the benefit of this therapeutic strategy in a randomized placebo-controlled trial.

Results of our study suggest that lamivudine should henceforth be prescribed as the antiviral agent of choice for HBV-PAN. This recommendation is in agreement with the results of large therapeutic trials on patients with chronic HBV infection that documented lamivudine as an effective and safe therapy for chronic hepatitis B (14–16). Compared with interferon-2α, lamivudine yields similar HBeAg seroconversion rates and offers additional advantages, i.e., oral administration, fewer side effects (27), and a potentially more rapid antiviral effect. However, the emergence of virus subpopulations bearing the YMDD mutation, which has been associated with reduced HBV susceptibility to lamivudine, was detected in 14–32% of lamivudine recipients after 1 year of therapy (14–16). Thus, the appearance of mutants increases with the time of exposure to lamivudine (28) and particularly concerns prolonged therapies of >6 months (29). Because our protocol prescribed lamivudine for 6 months, this problem should not be of major concern in the setting of HBV-PAN.

Recent therapeutic trials on chronic HBV infection suggested that the combination of the 2 major antiviral agents, lamivudine and interferon-2α, might be more effective than either agent alone (27,30). Although those findings are still open to debate (31), they raise the question of whether combining lamivudine and interferon-2α might also be useful in HBV-PAN. Isolated case reports have indicated the efficacy of this antiviral combination against HBV-PAN, including 1 patient who had previously failed on interferon-2α alone (32,33). Further investigation is nonetheless warranted to assess adequately the benefit of this combined therapy for HBV.

The lingering question is, what therapeutic option should be adopted for patients not clinically responding to short-term corticosteroids followed by lamivudine and plasma exchange? Although no such case was observed in this trial, the decision of how to manage such therapeutic failures should be made after careful consideration of the severity of the vasculitis. For patients with mild or moderate PAN, it might be reasonable to attempt to add interferon-2α, although the inadequacy of the data now available on the efficacy of combining lamivudine and interferon-2α has to be kept in mind. For critically ill patients, however, it would appear justified to switch to a conventional immunosuppressive strategy with prolonged corticosteroids and cyclophosphamide. Given their potential deleterious effects on the underlying hepatitis, treatment with these agents should be as short as possible, but no clear recommendation can be given concerning the optimal duration. Based on observations in chronic HBV carriers receiving cytotoxic agents, maintenance of lamivudine prophylaxis should then be considered to prevent HBV activation (34).

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REFERENCES

1. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides: proposal of an international consensus conference. Arthritis Rheum 1994; 37:187–92.
2. Gocke DJ, Hsu K, Morgan C, Bombardieri S, Lockshin M, Christian CL. Association between polyarteritis and Australia antigen. Lancet 1970;2:1149–53.
3. McMahon BJ, Heyward WL, Templin DW, Clement D, Lanier AP. Hepatitis B-associated polyarteritis nodosa in Alaskan Eskimos: clinical and epidemiologic features and long-term follow-up. Hepatology 1989;9:97–101.
4. Trépo C, Thivolet J. Hepatitis associated antigen and periarteritis nodosa (PAN). Vox Sang 1970;19:410–1.
5. Mahr A, Guillevin L, Poissonnet M, Aymé S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis and Churg-Strauss syndrome in a French urban population in 2000: a capture-recapture estimate. Arthritis Rheum 2004;51:92–9.
6. Hoofnagle JH, Davis GL, Pappas SC, Hanson RG, Peters M, Avigan MI, et al. A short course of prednisolone in chronic type B hepatitis: report of a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1986;104:12–7.
7. Cheng AL. Steroid-free chemotherapy decreases the risk of hepatitis flare-up in hepatitis B virus carriers with non-Hodgkin's lymphoma [letter]. Blood 1996;87:1202.
8. Hess G, Manns M, Hutteroth TH, Meyer zum Buschenfelde KH. Discontinuation of immunosuppressive therapy in hepatitis B surface antigen-positive chronic hepatitis: effect on viral replication and on liver cell damage. Digestion 1987;36: 47–54.
9. Chemotherapy and hepatitis B [editorial]. Lancet 1989;2: 1136–7.
10. Trépo C, Ouzan D, Delmont J, Tremisi J. [Superiority of a new etiopathogenic treatment curing periarteritis nodosa caused by hepatitis B virus, using a combination of brief corticotherapy, vidarabine and plasma exchange]. In French. Presse Méd 1988;17:1527–31.
11. Guillevin L, Merrouche Y, Gayraud M, Jarrousse B, Royer I, Leon A, et al. Périartérite noueuse due au virus de l'hépatite B: détermination d'une nouvelle stratégie thérapeutique chez 13 patients. Presse Méd 1988;17:1522–6.
12. Guillevin L, Lhote F, Léon A, Fauvelle F, Vivitski L, Trepo C. Treatment of polyarteritis nodosa related to hepatitis B virus with short term steroid therapy associated with antiviral agents and plasma exchanges: a prospective trial in 33 patients. J Rheumatol 1993;20:289–98.

13. Guillevin L, Lhote F, Sauvaget F, Deblois P, Rossi F, Levallois D, et al. Treatment of polyarteritis nodosa related to hepatitis B virus with interferon-alpha and plasma exchanges. Ann Rheum Dis 1994;53:334–7.
14. Tassopoulos NC, Volpes R, Pastore G, Heathcote J, Buti M, Goldin RD, et al, Lamivudine Precore Mutant Study Group. Efficacy of lamivudine in patients with hepatitis Be antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B. Hepatology 1999;29:889–96.
15. Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, et al, Asia Hepatitis Lamivudine Study Group. A one-year trial of lamivudine for chronic hepatitis B. N Engl J Med 1998;339: 61–8.
16. Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. N Engl J Med 1999;341:1256–63.
17. Nakhoul F, Gelman R, Green J, Khankin E, Baruch Y. Lamivudine therapy for severe acute hepatitis B virus infection after renal transplantation: case report and literature review. Transplant Proc 2001;33:2948–9.
18. Castells L, Vargas V, Rodriguez F, Allende H, Buti M, Sanchez-Avila JF, et al. Clinical impact and efficacy of lamivudine therapy in de novo hepatitis B infection after liver transplantation. Liver Transpl 2002;8:892–900.
19. Torii N, Hasegawa K, Ogawa M, Hashimo E, Hayashi N. Effectiveness and long-term outcome of lamivudine therapy for acute hepatitis B. Hepatol Res 2002;24:34–41.
20. Lightfoot RW Jr, Michel BA, Bloch DA, Hunder GG, Zvaifler NJ, McShane DJ, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. Arthritis Rheum 1990;33:1088–93.
21. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome: a prospective study in 342 patients. Medicine (Baltimore) 1996;75:17–28.
22. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
23. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981;1:431–5.
24. Prince AM, Trepo C. Role of immune complexes involving SH antigen in pathogenesis of chronic active hepatitis and polyarteritis nodosa. Lancet 1971;1:1309–12.
25. Guillevin L, Lhote F, Cohen P, Sauvaget F, Jarrousse B, Lortholary O, et al. Polyarteritis nodosa related to hepatitis B virus: a prospective study with long-term observation of 41 patients. Medicine (Baltimore) 1995;74:238–53.
26. McMahon BJ, Alward WL, Hall DB, Heyward WL, Bender TR, Francis DP, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis 1985;151:599–603.
27. Schalm SW, Heathcote J, Cianciara J, Farrell G, Sherman M, Willems B, et al. Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomised trial. Gut 2000;46:562–8.
28. Leung NW, Lai CL, Chang TT, Guan R, Lee CM, Ng KY, et al. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis Be antigen seroconversion rates: results after 3 years of therapy. Hepatology 2001;33:1527–32.
29. Seta T, Yokosuka O, Imazeki F, Tagawa M, Saisho H. Emergence of YMDD motif mutants of hepatitis B virus during lamivudine treatment of immunocompetent type B hepatitis patients. J Med Virol 2000;60:8–16.
30. Barbaro G, Zechini F, Pellicelli AM, Francavilla R, Scotto G, Bacca D, et al. Long-term efficacy of interferon alpha-2b and lamivudine in combination compared to lamivudine monotherapy in patients with chronic hepatitis B: an Italian multicenter, randomized trial. J Hepatol 2001;35:406–11.
31. Yang SS, Hsu CT, Hu JT, Lai YC, Wu CH. Lamivudine does not increase the efficacy of interferon in the treatment of mutant type chronic viral hepatitis B. World J Gastroenterol 2002;8:868–71.
32. Wicki J, Olivieri J, Pizzolato G, Sarasin F, Guillevin L, Dayer JM, et al. Successful treatment of polyarteritis nodosa related to hepatitis B virus with a combination of lamivudine and interferon alpha. Rheumatology 1999;38:183–5.
33. Erhardt A, Sagir A, Guillevin L, Neuen-Jacob E, Haussinger D. Successful treatment of hepatitis B virus associated polyarteritis nodosa with a combination of prednisolone, alpha-interferon and lamivudine. J Hepatol 2000;33:677–83.
34. Shibolet O, Ilan Y, Gillis S, Hubert A, Shouval D, Safadi R. Lamivudine therapy for prevention of immunosuppressive-induced hepatitis B virus reactivation in hepatitis B surface antigen carriers. Blood 2002;100:391–6.