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Sustained Clinical Improvement of a Patient with Decompensated Hepatitis B Virus-Related Cirrhosis after Treatment with Lamivudine Monotherapy

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Nagasaki, F., Ueno, Y., Yamamoto, T., Nakagomi, Y., Kido, O., Kakazu, E., Matsuda, Y., Kogure, T., Yamagiwa, Y., Kikuchi, K., Fukushima, K., Kanno, N., Niitsuma, H. and Shimosegawa, T. *Sustained Clinical Improvement of a Patient with Decompensated Hepatitis B Virus-Related Cirrhosis after Treatment with Lamivudine Monotherapy.* Tohoku J. Exp. Med., 2006, **210** (1), 29-36 —— Hepatitis B virus (HBV) infection, which causes liver cirrhosis and hepatocellular carcinoma, remains a major health problem in Asian countries. Recent development of vaccine for prevention is reported to be successful in reducing the size of chronically infected carriers, although the standard medical therapies have not been established up to now. In this report, we encountered a patient with decompensated HBV-related cirrhosis who exhibited the dramatic improvements after antiviral therapy. The patient was a 50-year-old woman. Previous conventional medical treatments were not effective for this patient, thus this patient had been referred to our hospital. However, the administration of lamivudine, a reverse transcriptase inhibitor, for 23 months dramatically improved her liver severity. During this period, no drug resistant mutant HBV emerged, and the serum HBV-DNA level was continuously suppressed. These virological responses were also maintained even after the antiviral therapy was discontinued. Moreover, both hepatitis B surface antigen and e antigen were observed to have disappeared in this patient. The administration of lamivudine to patients with HBV-related cirrhosis, like our present case, should be considered as an initial medical therapeutic option, especially in countries where liver transplantation is not reliably available. ———— chronic hepatitis; HBV; lamivudine

Hepatitis B virus (HBV) infection is an etiologic agent of liver cirrhosis and hepatocellular carcinoma, and it remains a major health problem worldwide, especially in Asian countries (Lee 1997).

The HBV infection ranges with a wide vari-

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ety of types in the natural clinical spectrum. Approximately 15 to 40% of all patients with chronic Hepatitis B virus (HBV) infection are expected to progress to liver cirrhosis and terminal stage liver disease (Maddrey 2000).

Eight different genotypes of HBV, named A - H, have been determined to date (Okamoto et al. 1987, 1988; Norder et al. 1992; Stuyver et al. 2000; Arauz-Ruiz et al. 2002). Moreover, the clinical outcomes are reported to vary according to HBV genotypes. For example, as for genotype B (HBV/B) and C (HBV/C), which are characteristic of Asia, HBV/B causes seroconversion more frequently than HBV/C, and those infected with HBV/B appear to have a better prognosis (Kikuchi 2000; Orito et al. 2001).

Lamivudine, an orally administered nucleotide analogue, is known for its safety and effectiveness for the treatment of patients with chronic HBV infection, including HBV cirrhosis. Its effects are known to include, not only for the inhibition of HBV replication but also the improvement of liver disease severity (Dienstag et al. 1999a; Leung et al. 2001).

We encountered a patient with decompensated HBV cirrhosis. Her clinical data had gradually deteriorated, but she showed a dramatic clinical improvement after the administration of lamivudine for 23 months. In addition, this clinical improvement was maintained even after the medication was stopped, thus resulting in the clearance of the HBV surface antigen (HBs Antigen).

Patient

The patient was a 50-year-old female. She was a housewife and had no special past medical history, including any blood transfusions. She did not have a habit of drinking alcohol, smoking, or any usual drugs.

Clinical course

She was pointed out to have a liver dysfunction for the first time at a health check-up held in April 1997. Afterwards, she became aware of general fatigue and edema of the legs, and she saw a physician for a treatment. As for her laboratory findings on February 26th in 1998, HBs Ag was positive and the serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were 235 IU/L and 211 IU/L, respectively. She was diagnosed to be an HBV carrier at that time. She was thereafter administered oral diuretics for a while. During this period, the serum levels of AST and ALT showed 100~250 IU/l, and AST was continuously dominant.

Thereafter, she was pointed out to have conjunctiva icterus, and thus was referred to the previous hospital on May 10, 1999. The serum tests at admission are shown in Table 1. It turned out that her current status was terminal stage liver disease, namely decompensated HBV cirrhosis. HBV-DNA was monitored by a branched DNA amplification assay in those days. Its cut-off for HBV viremia was 7×10^5 equivalents per ml. She was negative for antibody to hepatitis C virus, human immunodeficiency virus, and she was also negative for anti-nuclear antibody and anti-mitochondria antibody.

She was admitted to the hospital one week later. Her consciousness was clear but she showed icterus. She just only complained of general malaise. Abdominal computed tomography demonstrated neither ascites nor a liver tumor, but a chronic liver disease pattern. Endoscopic screening showed the presence of esophageal varices. These findings suggested her poor prognosis and also further supported the urgent need for treatment to prevent any further liver damages.

She was transfused fresh frozen plasma and albumin. Additional diuretics were administered orally. Despite the administration of these therapies for four months, her general condition and laboratory data did not show any remarkable improvement.

She was finally discharged from the first hospital, and was referred to our hospital on September 27, 1999. The laboratory findings at admission to our hospital are shown in Table 2. She was icteric but demonstrated a vascular spider, however, edema of the legs was not observed. Regarding liver cirrhosis, the Child-Pugh score was 10 points, i.e., grade C. In addition, regarding HBV infection, it had not seroconverted from hepatitis B e (HBe) antigen to anti-HBe positive

TABLE 1. Clinical findings at the first visit to the previous hospital (September 19, 2000).

WBC	7.0×10^3	/μl	RBC	3.09×10^6	/μl
Hb	12.0	g/dl	Plt	74×10^3	/μl
PT	37.7	%			
T.Bil	4.9	mg/dl	Direct Bil	2.5	mg/dl
AST	86	IU/l	ALT	72	IU/l
ALP	686	IU/l	GGTP	36	IU/l
LDH	578	IU/l	ChE	67	IU/l
ZTT	38.4	Kunkel	TTT	34.3	Kunkel
BUN	12	mg/dl	Creatinine	0.6	mg/dl
Total protein	6.8	g/dl	Albumin	2.4	g/dl
Total cholesterol	141	mg/dl	Triglyceride	55	mg/dl
Na	140	mEq/l	K	2.6	mEq/l
Cl	103	mEq/l			
AFP	29	ng/dl			
ANA	Negative		AMA	Negative	
HBs-Ag	Positive		Anti-HBs	Negative	
HBe-Ag	Positive		Anti-HBe	Negative	
HBV-DNA	200	Meq/ml			
anti-HCV	Negative				

WBC, white blood cell; PT, prothrombin time; T.Bil, total bilirubin; AST, asparate aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenate; ZTT, zincsulfate turbidity test; BUN, blood urea nitrogen; AFP, alpha feto protein; ANA, anti nuclear antibody; RBC, red blood cell; Plt, platelet; Direct Bil, direct bilirubin; ALT, alanine aminotransferase; GGTP, gamma glutamil transpeptidase; ChE, choline esterase; TTT, thymol turbidity; AMA, anti mitochondria antibody.

yet, and the genotype was C. Regarding her general condition including age, HBV genotype, HBe antigen positive, presence of cirrhosis, and efficacies of the previous general medical treatments, she was therefore predicted to demonstrate a poor clinical course unless she received antiviral treatments or liver transplantation.

We explained the above treatment strategies to her, and she desired the former therapy. We started to administer lamivudine 50 mg per day on October 4th after obtaining the patient's informed consent in order to prevent a progression of liver failure. Later, lamivudine was administered at a dose of 100 mg per day.

Thereafter, her serum HBV-DNA level gradually decreased after about one month of treatment, thus leading to almost an undetectable level, which was thereafter sustained. It was accompanied by a decrease in the serum level of AST and ALT. In contrast, the serum albumin level increased, as shown in Fig. 1.

We performed a laparoscopic liver biopsy on June 13, 2000. The macroscopic and microscopic findings are shown in Fig. 2. Both of them showed a liver cirrhosis pattern, but the patient's recovery from the disease was confirmed.

She showed no flare up of either the serum HBV-DNA levels or liver function during the treatment course, and her laboratory tests remarkably improved as shown in Table 3. Twenty-three-month treatment regimen led the patient to become not only HBe antigen negative but also HBs antigen negative. We finally stopped the administration of lamivudine on July 10, 2001.

At present, 50 months have passed since the cessation of the medication, but the serum HBV-DNA level is still at an undetectable level based on a polymerase chain reaction (PCR) assay (its

TABLE 2. Clinical findings at the first visit to our hospital (September 27, 1999).

WBC	3.9×10^3	/μl	RBC	3.28×10^6	/μl
Hb	12.5	g/dl	Plt	72×10^3	/μl
PT	46.3	%			
T.Bil	3.5	mg/dl	D.Bil	1.8	mg/dl
AST	74	IU/l	GGTP	36	IU/l
ALP	519	IU/l	ALT	50	IU/l
LDH	461	IU/l	ChE	79	IU/l
ZTT	33.1	Kunkel	TTT	33.1	Kunkel
BUN	11	mg/dl	Creatinine	0.6	mg/dl
Total protein	7.6	g/dl	Albumin	3.1	g/dl
Total cholesterol	151	mg/dl	Triglyceride	61	mg/dl
Na	136	mEq/l	K	4.2	mEq/l
Cl	104	mEq/l			
HBs-Ag	Positive		Anti-HBs	Negative	
HBe-Ag	Positive		Anti-HBe	Negative	
HBV-DNA	99	Meq/ml	Genotype	C	

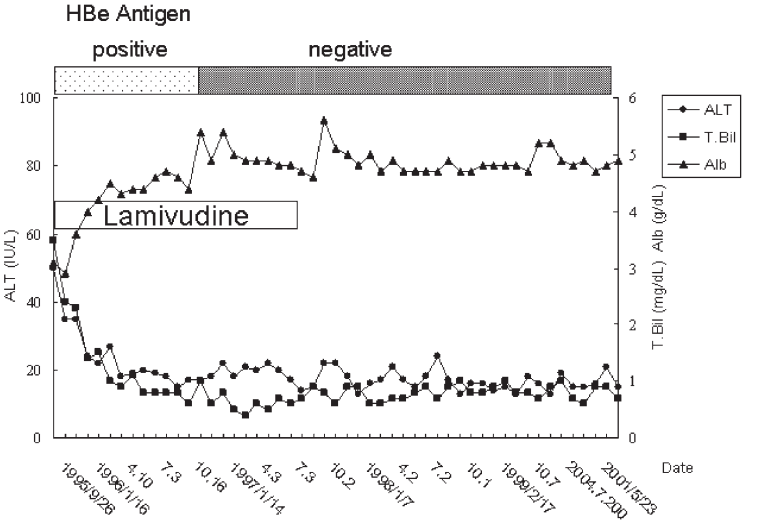

Fig. 1. The clinical course of the 50-year-old female with decompensated liver cirrhosis due to a hepatitis B virus infection. As shown in the figure, the administration of lamivudine improved her hepatic function. The serum HBV-DNA has been kept undetectable level ever since November 1999.

cut-off for HBV viraemia was $10^{2.6}$ copies per ml) and the serum liver function tests are all within the normal limits. Moreover, her HBs antigen has disappeared and anti HBs has emerged.

The patient with decompensated HBV cirrhosis therefore showed a dramatically successful clinical course.

DISCUSSION

A chronic HBV infection is one of the major health problems in Asian countries, and HBV/B and HBV/C are dominantly detected in this region. As we previously reported, HBV/B has been found to cause HBe seroconversion more

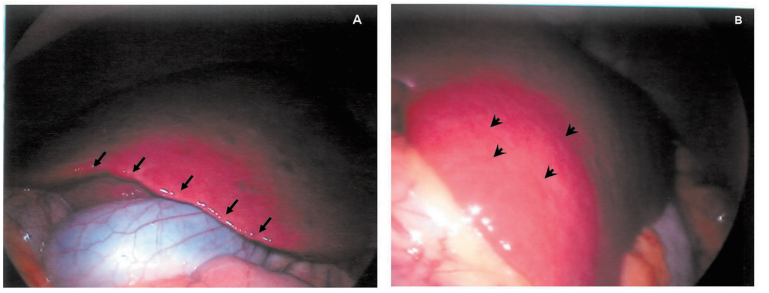

Fig. 2. Macroscopic view of the right robe (A) and left lobe (B) of the liver. Laparoscopy was performed on June 13th in 2000. The administration of lamivudine enabled to perform the liver biopsy due to the improvement of her coagulopathy. As shown in panel A, the edge of the liver was slightly dull (arrows) and the liver surface was moderately hard. As shown in panel B, no nodular formation was apparent (arrow heads). These findings do not indicate the presence of apparent liver cirrhosis.

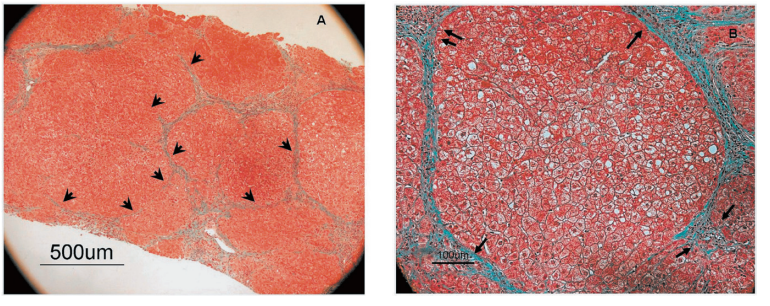

Fig. 3. Microscopic pathological findings. With low power-view (A), the liver specimens showed established cirrhotic pattern. As shown in high-power view (B), the inflammatory cells were absent (arrow). Also, the collagen fibers, bridging a portal area to a central vein or portal to portal area, had been absorbed and also had become thinner (arrow head). The biopsy was compatible with the resolution phase of liver cirrhosis (The bar indicates 500 μm in [A] and 100 μm in [B]).

frequently than HBV/C, and those infected with HBV/B are also known to show good prognoses (Kikuchi et al. 2000; Orito et al. 2001).

In this report, we encountered a 50-year-old female patient with decompensated HBV cirrhosis. She did not have other factors which affected her previous poor clinical course, such as an overconsumption of alcohol, co-infection of hepatitis C virus or human immunodeficiency virus, or the use of any other immunosuppressive agents. As a result, the only explanation for her severe clinical course was the fact that the genotype of this specific patient was genotype C which was known to have more aggressive natural course compared to other HBV genotypes.

Nevertheless, 23-month administration of lamivudine successfully led to the prevention of a progression of the severe liver damage, while also resulting in an improvement of the decompensated liver cirrhosis. As for the Child-Pugh score, it improved from 10 points to 5 points, i.e., grade C to grade A at last. Finally, the administration of lamivudine could be stopped due to the remarkably effective clinical results.

Although both of these therapies, namely liver transplantation and the administration of lamivudine to HBV carriers were not common in Japan those days, she nevertheless made a good choice in selecting this treatment regimen. Without one of these treatment options, the patient would most likely not have recovered. We have ever encountered some patients with severe liver failure derived from various causes, who had been difficult to rescue other than liver transplan-

Table 3. Clinical findings at the latest visit to our hospital as an outpatient (May 24, 2005).

WBC	4.8×10^3	/μl	RBC	4.61×10^6	/μl
Hb	14.9	g/dl	Plt	183×10^3	/μl
PT	81.0	%			
T.Bil	0.9	mg/dl	Direct Bil	0.1	mg/dl
AST	24	IU/l	ALT	21	IU/l
ALP	288	IU/l	GGTP	19	IU/l
LDH	197	IU/l	ChE	373	IU/l
ZTT	6.1	Kunkel	TTT	5.4	Kunkel
BUN	16	mg/dl	Creatinine	0.7	mg/dl
Total protein	7.7	g/dl	Albumin	4.8	g/dl
Total cholesterol	221	mg/dl	Triglyceride	100	mg/dl
Na	144	mEq/l	K	4.0	mEq/l
Cl	104	mEq/l			
AFP	1.6	ng/dl			
HBs-Ag	negative		Anti-HBs	Positive	
HBe-Ag	negative		Anti-HBe	Positive	
HBV-DNA	< 2.6	Log copy/ml			

tation (Nagasaki et al. 2005). Nevertheless, as for HBV carriers, lamivudine could be one of the most useful therapeutic options for patients including severe liver failure.

In general, lamivudine is known to be a safe and effective treatment, but its usage over a long period can lead to the emergence of a drug resistant mutant virus, while on the other hand, the cessation of this medication is also difficult because of the danger of a post-treatment flare-up (Dienstag et al. 1999a; Leung et al. 2001).

The administration of lamivudine is well known to improve liver damage of even recipient patients with decompensated HBV cirrhosis or hepatocellular carcinoma for liver transplantation.

On the other hand, for patients with decompensated HBV cirrhosis, it is not always an appropriate treatment because of the following three reasons: First, it has been reported to take at least 6 months for any remarkable clinical improvement to be observed (Villeneuve et al. 2000; Yao et al. 2001). Second, the long duration lamivudine therapy can also lead to the emergence of drug-resistant mutants, which might thus lead to hepatic failure, i.e., breakthrough hepatitis among some patients (Liaw et al. 2000). Third, in contrast to the occurrence of breakthrough hepatitis, after the discontinuation of the drug with short term period therapy, the serum HBV-DNA tends to return to pre-treatment levels over the long term, and some patients can develop hepatitis, i.e., the post-treatment flare up (Kapoor et al. 2000; Santantonio et al. 2000). Actually, the ideal duration of lamivudine treatment still remains controversial, especially for the patients with developed liver diseases derived from an HBV infection, because of the risk of either breakthrough hepatitis or a post-treatment flare up, both of which might lead to fatal liver failure.

A cessation of lamivudine administration may be considered in patients who show a remarkable clinical effect, thus leading to an improvement of the liver function. The latest clinical findings of our patient showed a complete resolution of liver function, which seemed to be sufficient enough for possible flare up. In this case, the clinical improvements after the administration of lamivudine were quite similar to those of previous reports (Dienstag et al. 1999b), but the improvements were maintained even after the cessation of the drug, thus finally resulting in the disappearance of HBs Ag.

The patient was refractory to all previous general internal medical therapies, thus her clinical course seemed to be classified as the most severe decompensated liver cirrhosis phase. The administration of lamivudine obviously improved her liver damage, and she might not have been cured without the therapy. In this case, the good clinical course after the administration of lamivudine might have been due to the appropriate duration of the therapy. The 23-month administration period in our case was not too long to induce drug resistant mutation of HBV, although the recovery of liver function during this period was endurable to post-treatment flare up.

Nevertheless, we should continue to closely monitor this patient for any possible relapse and surveillance for hepatocellular carcinoma. As for hepatocellular carcinoma, its risk among HBV carriers tends to depend on HBV replication and liver severity. In HBV carriers with a normal ALT level, the risk of hepatocellular carcinoma is lower than that of HBV carriers with active HBV replication (0.5% vs 2 to 5%, annually) (Yang et al. 2002). Although she was negative for both HBs antigen and HBe antigen, we should continue to conduct a close surveillance for hepatocellular carcinoma using a combination of serum tumor markers, such as alpha-fetoprotein, des-gamma-carboxyprothrombin and ultrasound, and computed tomography.

We do not have any clear explanation regarding which patients with HBV cirrhosis administered with lamivudine may also demonstrate such dramatic clinical improvement prior to the treatment. Further studies regarding the clinical relevance and characteristics of the HBV genome are required to predict the most effective usage of lamivudine for patients with HBV infection, including decompensated liver cirrhosis and hepatocellular carcinoma. The usage of lamivudine in cases such as our patient should thus be considered as an additional medical therapeutic option, especially in countries where liver transplantation is still not readily available such as Japan. In fact, liver transplantations performed in Japan have been namely living donor transplantation. It is often difficult to nominate the donors for transplantations. We previously described such experiences in living donor liver transplantation for fulminant hepatitis caused by HBV infection (Inoue et al. 2005). Thus, the administration of lamivudine seems first line treatment for decompensated liver cirrhosis caused by HBV infection.

References

Arauz-Ruiz, P., Norder, H., Robertson, B.H. & Magnius, L.O. (2002) Genotype h: A new amerindian genotype of hepatitis B virus revealed in central america. *J. Gen. Virol.*, **83**, 2059-2073.

Dienstag, J.L., Schiff, E.R., Mitchell, M., Casey, D.E., Jr., Gitlin, N., Lissoos, T., Gelb, L.D., Condreay, L., Crowther, L., Rubin, M. & Brown, N. (1999a) Extended lamivudine retreatment for chronic hepatitis B: Maintenance of viral suppression after discontinuation of therapy. *Hepatology*, **30**, 1082-1087.

Dienstag, J.L., Schiff, E.R., Wright, T.L., Perrillo, R.P., Hann, H.W., Goodman, Z., Crowther, L., Condreay, L.D., Woessner, M., Rubin, M. & Brown, N.A. (1999b) Lamivudine as initial treatment for chronic hepatitis B in the united states. *N. Engl. J. Med.*, **341**, 1256-1263.

Inoue, J., Ueno, Y., Kanno, N., Anzai, H., Kondo, Y., Moritoki, Y., Mikami, E., Chiba, M., Kogure, T., Nagasaki, F., Fukushima, K., Iwasaki, T., Satomi, S. & Shimosegawa, T. (2005) Living related liver transplantation for acute fulminant hepatitis B: Experience from two possible hyper-acute cases. *Tohoku J. Exp. Med.*, **205**, 197-204.

Kapoor, D., Guptan, R.C., Wakil, S.M., Kazim, S.N., Kaul, R., Agarwal, S.R., Raisuddin, S., Hasnain, S.E. & Sarin, S.K. (2000) Beneficial effects of lamivudine in hepatitis B virus-related decompensated cirrhosis. *J. Hepatol.*, **33**, 308-312.

Kikuchi, K., Niitsuma, H., Ishii, M., Julieta, G. C., Shang, H., Ojima, T., Suzuki, C., Kobayashi, T., Ueno, Y., Kobayashi, K., Shimosegawa, T. & Toyota, T. (2000) Genoepidemiology and its relationship to clinical features in patients infected chronically with hepatitis B virus (HBV). *Hepatol. Res.*, **17**, 43-55.

Lee, W.M. (1997) Hepatitis B virus infection. *N. Engl. J. Med.*, **337**, 1733-1745.

Leung, N.W., Lai, C.L., Chang, T.T., Guan, R., Lee, C.M., Ng, K.Y., Lim, S.G., Wu, P.C., Dent, J.C., Edmundson, S., Condreay, L.D. & Chien, R.N. (2001) Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: Results after 3 years of therapy. *Hepatology*, **33**, 1527-1532.

Liaw, Y.F., Leung, N.W., Chang, T.T., Guan, R., Tai, D.I., Ng, K.Y., Chien, R.N., Dent, J., Roman, L., Edmundson, S. & Lai, C.L. (2000) Effects of extended lamivudine therapy in asian patients with chronic hepatitis B. Asia hepatitis lamivudine study group. *Gastroenterology*, **119**, 172-180.

Maddrey, W.C. (2000) Hepatitis B: An important public health issue. *J. Med. Virol.*, **61**, 362-366.

Nagasaki, F., Ueno, Y., Mano, Y., Igarashi, T., Yahagi, K., Niitsuma, H., Okamoto, H. & Shimosegawa, T. (2005) A patient with clinical features of acute hepatitis E viral infection and autoimmune hepatitis. *Tohoku J. Exp. Med.*, **206**, 173-179.

Norder, H., Hammas, B., Lofdahl, S., Courouce, A.M. &

Magnius, L.O. (1992) Comparison of the amino acid sequences of nine different serotypes of hepatitis B surface antigen and genomic classification of the corresponding hepatitis B virus strains. *J. Gen. Virol.*, **73**, 1201-1208.

Okamoto, H., Imai, M., Tsuda, F., Tanaka, T., Miyakawa, Y. & Mayumi, M. (1987) Point mutation in the S gene of hepatitis B virus for a d/y or w/r subtypic change in two blood donors carrying a surface antigen of compound subtype adyr or adwr. *J. Virol.*, **61**, 3030-3034.

Okamoto, H., Tsuda, F., Sakugawa, H., Sastrosoewignjo, R.I., Imai, M., Miyakawa, Y. & Mayumi, M. (1988) Typing hepatitis B virus by homology in nucleotide sequence: Comparison of surface antigen subtypes. *J. Gen. Virol.*, **69**, 2575-2583.

Orito, E., Mizokami, M., Sakugawa, H., Michitaka, K., Ishikawa, K., Ichida, T., Okanoue, T., Yotsuyanagi, H. & Iino, S. (2001) A case-control study for clinical and molecular biological differences between hepatitis B viruses of genotypes B and C. Japan HBV genotype research group. *Hepatology*, **33**, 218-223.

Santantonio, T., Mazzola, M., Iacovazzi, T., Miglietta, A., Guastadisegni, A. & Pastore, G. (2000) Long-term follow-up of patients with anti-hbe/hbv DNA-positive chronic hepatitis B treated for 12 months with lamivudine. *J. Hepatol.*, **32**, 300-306.

Stuyver, L., De Gendt, S., Van Geyt, C., Zoulim, F., Fried, M., Schinazi, R.F. & Rossau, R. (2000) A new genotype of hepatitis B virus: Complete genome and phylogenetic relatedness. *J. Gen. Virol.*, **81**, 67-74.

Villeneuve, J.P., Condreay, L.D., Willems, B., Pomier-Layrargues, G., Fenyves, D., Bilodeau, M., Leduc, R., Peltekian, K., Wong, F., Margulies, M. & Heathcote, E.J. (2000) Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. *Hepatology*, **31**, 207-210.

Yang, H.I., Lu, S.N., Liaw, Y.F., You, S.L., Sun, C.A., Wang, L.Y., Hsiao, C.K., Chen, P.J., Chen, D.S. & Chen, C.J. (2002) Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N. Engl. J. Med.*, **347**, 168-174.

Yao, F.Y., Terrault, N.A., Freise, C., Maslow, L. & Bass, N.M. (2001) Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating hepatitis B infection awaiting liver transplantation: A comparative study using a matched, untreated cohort. *Hepatology*, **34**, 411-416.