Retransplantation for Precore Mutant-Related Chronic Hepatitis B Infection: Prolonged Survival in a Patient Receiving Sequential Ganciclovir/Famciclovir Therapy

Geoffrey McCaughan, Peter Angus,† Scott Bowden,‡ Tim Shaw,‡ Allan Breschkin,‡ Ross Sheil,* and Stephen Locarnini‡*

Retransplantation for hepatitis B–related liver allograft failure is rarely successful. Recurrence of infection is almost universal, and the second allograft is invariably lost more rapidly than the first. In a recent multicenter study, only 1 of 20 hepatitis B virus (HBV)–positive patients who underwent liver retransplantation survived beyond 6 months. This report describes the long-term effect of antiviral therapy in a 56-year-old man who was retransplanted for HBV-related allograft loss 14 months after his initial liver transplant. He was treated after the second transplant with intravenous daily ganciclovir. After 10 months of this therapy HBV recurrence was detected. After a change to oral famciclovir therapy, there was a decrease in serum HBV DNA and aminotransferase levels and an improvement in the patient's clinical condition. Famciclovir therapy has now been continued for 26 months, and the patient remains well 3 years after his second transplant, despite persistent HBV infection and progression to cirrhosis. These observations indicate that the use of long-term antiviral therapy offers promise for improving outcomes in patients who undergo retransplantation after HBV-related liver allograft failure.

Copyright © 1996 by the American Association for the Study of Liver Diseases

Liver transplantation for hepatitis B virus (HBV)–associated cirrhosis has had limited success mainly because of the high incidence of HBV recurrence in the allograft.[1] Unfortunately, retransplantation for HBV-related disease is even less successful and is usually followed by more rapid graft loss than occurs following the first transplant.[2] The case report describes the treatment with the nucleoside analogues ganciclovir and famciclovir of a patient retransplanted due to HBV recurrence.

Case Report

A 57-year-old white male with hepatitis B virus (HBV)–associated cirrhosis and progressive liver failure underwent transplantation in June 1991. He was treated postoperatively with daily anti–hepatitis B surface antigen (HBs) hyperimmune globulin (HBIG) at a dose of 400 IU intramuscularly for 1 week, then 400/IU weekly for 1 month, and then 400/IU monthly until HBsAg was detected by immunoassay in serum. Titers of anti-HBs were not measured. At the time of transplantation he was HBsAg positive, HBV DNA positive (150 pg/mL by the Digene Hybrid Capture Assay, Digene Diagnostics, Beltsville, MD), hepatitis B e antigen (HBeAg) negative, and anti-HBe positive. Anti–hepatitis C virus and anti–delta virus antibodies were not detected. Sequencing of serum viral DNA indicated the presence of a mutation at nucleotide position 1896 (G to A conversion resulting in a stop codon in the precore region).[3] In December 1991 recurrence of HBsAg and HBV DNA in serum was noted with an alanine aminotransferase (ALT) elevation of 500 to 1000 U/L. Serum HBV DNA was present at 12,000 pg/mL as measured by the Digene Hybrid Capture Assay. He remained HBsAg positive, HBeAg negative, and anti-HBe positive, and repeat sequencing of the HBV precore region showed no change from the pretransplantation setting. By June 1992 he noticed increased ankle swelling, ascites, and the development of hepatic encephalopathy and subsequently underwent retransplantation in August 1992. Postoperatively, he was treated with intravenous ganciclovir (500 mg daily) via Hickman's catheter. He also received low dose HBIG as per the initial transplant protocol.

At the beginning of his 8th month of therapy (March 1993) HBsAg positivity and rising serum levels of HBV DNA and ALT levels were noted. In June 1993 ganciclovir therapy was stopped

*From the *A.W. Morrow Gastroenterology and Liver Centre and Australian National Liver Transplant Unit, Royal Prince Alfred Hospital, Camperdown; the †Victorian Liver Transplant Unit, Austin Hospital, Melbourne; and the ‡Victorian Infectious Diseases Reference Laboratory, Fairfield Hospital, Melbourne, Australia.*

Address reprint requests to GW McCaughan, AW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Missenden Road, Camperdown 2050, Australia.

Copyright © 1996 by the American Association for the Study of Liver Diseases

1074-3022/96/0206-1010$3.00/0

(total 10 months' therapy), and oral famciclovir therapy (Smith-Kline Beecham Pharmaceuticals, Australia) at 500 mg three times a day commenced. Following the introduction of famciclovir therapy, there was a progressive fall in his HBV DNA and ALT levels, although the ALT level never returned to normal. A liver biopsy specimen in September 1993 (month 13, Fig. 1) showed chronic hepatitis without cirrhosis. The patient had a subsequent flare of his HBV DNA and ALT levels for a 2-month period from September 1993 to November 1993 (months 13-15, Fig 1). In November 1993 (15 months after transplantation), a liver biopsy specimen showed chronic hepatitis with cirrhosis (absent 2 months earlier). Immunostaining of the biopsy specimen for HBsAg and HBeAg with monoclonal antibodies indicated strong expression of both these antigens in hepatocytes. HBsAg was detected in 50% of cells, and hepatitis B core antigen (HBcAg) showed cytoplasmic staining in 30% of cells.

Three pharmacokinetic studies were performed on this patient while he was being treated with famciclovir. The results, which are summarized in Table 1, indicate that famciclovir absorption and metabolism and/or penciclovir uptake and excretion were indicative of decreased clearance during December 1993 during the transient appearance of mild ascites and ankle edema. This followed the ALT and HBV DNA flare in September to November 1993. Famciclovir was subsequently reduced to a dosage of 500 mg twice a day. The patient's clinical condition improved over the next 2 to 3 months, and by June 1994 (22 months after transplantation, Fig. 1), a pharmacokinetic study showed increased clearance of the drug (Table 1), thus it was possible to reinstate famciclovir treatment at the original dosage (500 mg three times a day). In December 1995 the patient was alive and well with a normal serum albumin (44 g/L) and normal international normalized ratio (INR); (1.2). The patient was serum HBV DNA negative with an ALT between 50 to 110 U/L. A follow-up liver biopsy specimen still showed chronic active hepatitis with cirrhosis. Immunosuppressive therapy after retransplantation consisted of reducing doses of prednisone (7.5 mg until January 1994, 5 mg daily since then) and cyclosporine, 100 mg twice daily. His current medications are prednisone, 5 mg per day; cyclosporine A, 75 mg twice a day, and famciclovir therapy 500 mg, three times a day.

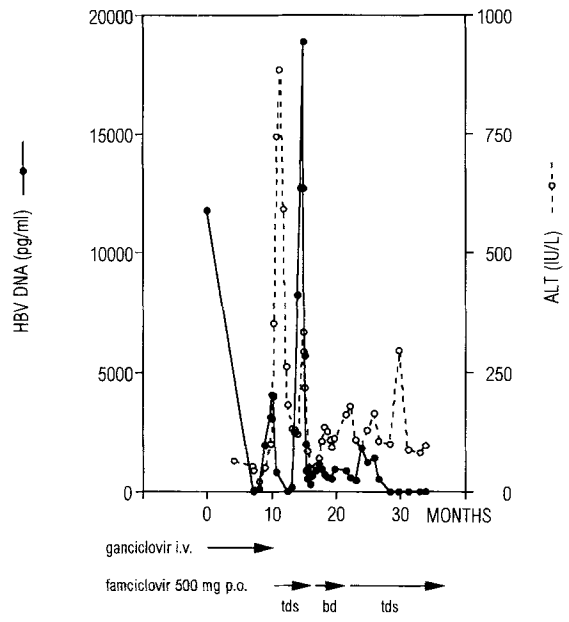

Figure 1. Serum HBV DNA and ALT levels over a 3-year period in the patient described. Point 0 represents time of retransplantation (8/8/92). If necessary, specimens were diluted prior to testing so that HBV DNA levels were within the assay linear range (10-2000 pg/mL); the concentration of HBV DNA in the original serum specimens was calculated allowing for the dilution factor used.

Discussion

A recent report confirmed that graft survival following retransplantation for HBV disease (mean 4 months) was inevitably shorter than for the primary graft (mean 14 months). Only 1 of 20 patients survived for longer than 6 months after retransplantations.[2] In another study, none of 7 patients survived retransplantation for recurrent HBV infection.[4] In contrast, there is a recent report of prolonged survival in a patient in whom reinfection was prevented by high dose HBIG therapy.[5]

The prolonged survival of our patient suggests that the combination of sequential antiviral therapy with ganciclovir and famciclovir may have contributed to improved outcome despite early HBV recurrence and rapid development of cirrhosis in the second graft. Both ganciclovir and famciclovir inhibit HBV DNA replication by blocking viral DNA chain elongation[6] and have been shown to be effective against duck and human HBV.[7-11] More recently, ganciclovir has been shown to be effective in some patients with HBV recurrence after liver transplantation.[12] However, progressive hepatic damage has been observed in a patient who received ganciclovir for HBV disease after liver transplantation despite a reduction in HBV DNA levels.[13]

It is of interest that intermittent fluctuations of ALT and HBV DNA occurred in our patient despite stable immunosuppressive and antiviral therapy. It is unclear whether the most significant fluctuation (months 13-15 posttransplant) represented immune activation or allograft dysfunction associated with increasing viral load. During this 2-month period there was progression to cirrhosis. However, following this flare, disease activity improved, and the patient remains alive and well with good hepatic

Table 1. Pharmacokinetic Parameters for Plasma Penciclovir Measured by Reverse Phase HPLC After a Single Oral 500-mg Dose of Famciclovir

Date	Months After Tx	C_{max} (μg/mL)	t_{max} (h)	AUC (μg/h/mL)	$t_{1/2}$ (h)	Serum creatinine (μmol/L)
September 1993	13	4.1	1.57	17.2	1.1	150
December 1993	16	11.0	2.95	88.7	2.0	160
June 1994	22	3.8	2.83	29.4	1.96	178
Normal values*		3.34 ± 0.58	0.75 • (0.5-1.0)	9.27 ± 2.18	2.27 ± 0.37	

Note: Pharmacokinetic parameters were calculated from the raw data with the computer package designed for curve-fitting, nonlinear regression analysis, and pharmacokinetic modeling (MINSQ II, version 1.02, Micromath Scientific Software, Salt Lake City, UT, USA).
Abbreviations: C_{max}, peak plasma concentration; t_{max}, time between administration and concentration peak; AUC, area under curve; $t_{1/2}$, elimination half-life; h, hours.
*Normal data from Ref 14 are shown for comparison. Values are mean (±SD) or • median (range).

synthetic function and is currently HBV DNA negative more than 3 years after retransplantation.

The role of antiviral therapy in prolonging graft survival in our patient, however, remains uncertain. One possibility is that it inhibited viral replication sufficiently to prevent the rapid progression of disease that occurred in the first graft. Controlled clinical trials will be required to establish clearly the role of these agents in prophylaxis and therapy of posttransplant HBV patients.

Acknowledgments

We would like to thank SmithKline Beecham Pty, Ltd, for access to famciclovir therapy, Rebecca de Jesus for secretarial assistance, and Carolyn Parsons for technical help.

References

1. Lake JR, Wright TL. Liver transplantation for patients with hepatitis B. What have we learned from our results? [Editorial] Hepatology 1991;13:796-799
2. Crippin J, Foster B, Carlen S, Borlich A, Bodenheimer H. Retransplantation in hepatitis B: A multicenter experience. Transplantation 1994;57:823-826
3. Angus P, Locarnini S, McCaughan GW, Jones R, Bowden S. Hepatitis B virus precore mutant infection is associated with severe recurrent disease following liver transplantation. Hepatology 1995;21:14-18
4. Devlin J, Smith HM, Portmann B, Tan KC, Williams R. Impact of immunoprophylaxis and patient selection on outcome of transplantation for HBsAg positive liver recipients. J Hepatol 1994;21:204
5. Kiyasu PK, Ishitani MB, McGory RW, Gaffey MJ, Dickson RC, Caldwell SH, Stevenson WC, Pruett TL. Prevention of hepatitis B "recurrence" after a second liver transplant: The role of maintenance polyclonal HBIG therapy. Transplantation 1994;58:954-955
6. Vere Hodge, RA. Review: Antiviral portrait series, number 3. Famciclovir and penciclovir. The mode of action of famciclovir including its conversion to penciclovir. Antiviral Chem Chemother 1993;4:67-84
7. Tsiguage KN, Slomka MJ, Maung M. Oral famciclovir against duck hepatitis B virus replication in hepatic and nonhepatic tissues of ducklings infected in ova. J Med Virol 1994;42:306-310
8. Boker KH, Ringe B, Kruger M, Pichlmagr R, Manns MP. Prostaglandin E plus famciclovir: A new concept for the treatment of severe hepatitis B after liver transplantation. Transplantation 1994;57:1706-1708
9. Angus P, Richards M, Bowden S, Ireton J, Sinclair R, Jones R, Locarnini S. Combination antiviral therapy controls severe post liver transplant recurrence of hepatitis B virus infection. J Gastro Hepatol 1993;8:353-355
10. Shaw T, Amor P, Civitico G, Boyd M, Locarnini S. In vitro antiviral activity of penciclovir, a novel purine nucleoside, against duck hepatitis B virus. Antimicrob Agents Chemother. 1994;38:719-723
11. Kruger M, Tillmann HL, Trautwein C, Oldhafter K, Boker KHW, Pichlmayr R, et al. Famciclovir treatment of hepatitis B virus recurrence after orthotopic liver transplantation: A pilot study. Hepatology 1995;22-A
12. Gish RG, Lau JYN, Brooks L, Fang JWS, Steady S, Imperial JI, et al. Ganciclovir treatment of hepatitis B virus infection in liver transplant recipients. Hepatology 1996;23:1-7
13. Yoshida EM, Wolber RA, Mahmood WA, Anderson FH, Scudamore CH, Erb SR. Attempted resolution of acute recurrent hepatitis B in a transplanted liver allograft by the administration of ganciclovir. Transplantation 1994; 58:956-958
14. Pue MA, Pratt SK, Fairless AJ, Fowles S, Laroche J, Georgiou P, Prince W. Linear pharmacokinetics of penciclovir following administration of single oral doses of famciclovir 125, 250 and 500 and 750 mg to healthy volunteers. J Antimicrob Chemother 1994;33:119-127