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Famciclovir treatment of hepatitis B infection following liver transplantation: a long-term, multi-centre study

Key words:
famciclovir; hepatitis B; liver transplantation; long-term study

Acknowledgments:
The authors acknowledge the following members of the *Famciclovir Liver Transplant Study Group: P. Angus, Austin Hospital, Heidelberg, Australia; M. Becker, Uniklinik Rudolf-Virchow, Berlin, Germany; P. Berg, Medizinische Klinik I Und Poliklinik, Universitaet Erlangen, Erlangen, Germany; P.H. Bernard, CHU De Bordeaux, Bordeaux, France; D. Bota-Fridlung, Hôpital De La Conception, Marseille, France; C. Broelsch, Universitaetskrankenhaus Hamburg–Eppendorf, Hamburg, Germany; M. Burdelski, Universitaetsklinik Pediatrics, Hamburg, Germany; Y. Calmus, C.H. Cochin, Paris, France; R.A. De Man, Academisch Ziekenhuis Rotterdam, Rotterdam, The Netherlands; S. Di Benedetto, Ospedale Sant'Orsola-Malpighi, Bologna, Italy; C. Duvoux, C.H. Henri Mondor, Creteil, France; A. Francavilla, Policlinico Di Bari, Bari, Italy; G.B. Gaeta, Ii Universita Di Napoli, Napoli, Italy; H. Hinrichsen, I. Medizinische Klinik, Kiel, Germany; P. Honore, Sart Tilman, Liege, Belgium; M.-C. Jung, Klinikum Grosshadern, Munich, Germany; H. Klinker, Med. Universitaetsklinik, Wuerzburg, Germany; G.A. Levy, Toronto General Hospital, Toronto, Canada; H. Lochs, Universitaetsklinik Charite, Berlin, Germany; P. Marcellin, Hopital Beaujon, Clichy, France; G. McCaughan, Royal Prince Alfred Hospital, Camperdown, Australia; P. Michielsen, UZA, Edegem, Belgium; J.P. Miguet, Hopital Jean Minjoz, Besancon, France; B. Roche, Centre Hepato-Biliaire, Hopital Paul Brousse, Villejuif, France; J.R. Siewert, Klinikum Rechts der Isar, Munich, Germany; U. Spengler, Medizinische Universitaetsklinik Venusberg, Bonn, Germany; I. Uhl, Universitaetsklinikum Rudolf-Virchow, Berlin, Germany; D. Vetter, CHRU Hopital Civil De Strasbourg, Strasbourg, France; J. Villeneuve, Hopital St. Luc, Montreal, Canada; T. Vogel, Medizinische Klinik Lebertransplantationsambulanz, Innsbruck, Austria; and, J.P. Zarski, Centre Hospitalier Universitaire De Grenoble, Grenoble, France. In addition, the data input and statistical analyses were performed by S. Wienecke and H. Collie, respectively, Focus Clinical Drug Development GMBH, Germany.

Abstract: Famciclovir is a novel guanosine nucleoside analogue with activity against herpes viruses and hepatitis B virus (HBV). Several preliminary reports have described efficacy of famciclovir in patients with recurrent hepatitis B after orthotopic liver transplantation (OLT). This report describes the largest study to date of long-term famciclovir treatment in patients with *de novo* or recurrent hepatitis B post-OLT. One hundred thirty patients with detectable serum HBV DNA after OLT received oral famciclovir 500 mg tid on a compassionate-use basis. Safety analyses included all treated patients; efficacy was assessed in all patients and a subgroup of 73 patients with complete baseline HBV DNA and alanine aminotransferase (ALT) data who had received ≥6 months of treatment. Efficacy parameters included serum levels of HBV DNA, ALT, and anti-HBe or anti-HBs seroconversion rates. Of the 70 patients treated for ≥6 months who could be evaluated for response/non-response to famciclovir, 52 (74%) were responders, defined as patients who experienced a 70% decrease or more in HBV DNA levels from baseline, or who became HBV DNA-negative, for at least two consecutive visits. In famciclovir responders, HBV DNA levels decreased by a median of 91% after 12 weeks of treatment, 95% after 6 months and >99% after 18 months of treatment. Marked differentiation between responders and non-responders could be made soon after the onset of treatment. Among anti-HBe positive patients with evidence of HBV replication, 12/13 were responders. Patients with high baseline ALT levels experienced more rapid suppression of HBV DNA during therapy with famciclovir. Famciclovir therapy was safe and well tolerated; serious adverse events were reported infrequently. Famciclovir treatment may be beneficial in patients with hepatitis B infection post-OLT.

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Following orthotopic liver transplantation (OLT) in patients with hepatitis B virus (HBV) infection, despite anti-HBs immunoprophylaxis, there is a high incidence of recurrence of HBV infection (1) which is further exacerbated by the use of immunosuppressive drugs to prevent graft rejection (2). These high rates of hepatitis B recurrence have led to the exclusion of chronic hepatitis B patients as potential OLT candidates in many centres in the past.

Received 22 October 1999, revised 9 August, accepted for publication 5 September 2000

Transplant Infectious Disease . ISSN 1398-2273

Transpl Infect Dis 2001: **3**: 16–23
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Until recently, interferon-α has been the standard treatment for chronic hepatitis B, and is successful in 25–40% of patients (3). Although interferon-α has been used to reduce viral load before transplantation, its use after transplantation is not generally recommended because it could induce allograft rejection (4) or stimulate an immune response to HBV, which could enhance hepatocyte damage in these patients (5). Prophylaxis with high-dose, long-term (6–12 months) or indefinite hepatitis B immunoglobulin (HBIG) has become the standard regimen used to prevent hepatitis B recurrence (1, 6). Efficacy of immunoprophylaxis has been poor in patients with active hepatitis B virus replication prior to transplantation, with HBV recurrence occurring in 83–100% of patients (1, 6).

Since patients in whom HBV recurrence occurs may develop graft failure as a result of progressive liver disease (1, 7), nucleoside analogues are being investigated to treat hepatitis B virus infections in transplant recipients. Lamivudine (2′,3′-dideoxy-3′-thiacytidine) is available for the treatment of chronic hepatitis B infection in many countries, while famciclovir, the oral pro-drug of penciclovir, is approved for treatment and suppression of genital herpes infections in immunocompetent and immunocompromised adults and treatment of acute herpes zoster. Both lamivudine and famciclovir have shown potent activity against HBV in cell culture (8, 9). Penciclovir inhibits DNA replication by inhibiting the priming step of single-stranded DNA synthesis. Penciclovir also inhibits DNA polymerase-catalysed chain elongation and, most importantly, reduces the levels of covalently closed circular (CCC) DNA responsible for maintaining viral replication in HBV-infected cells (10). Lamivudine inhibits DNA polymerase-catalysed chain extension (8). In clinical studies in immunocompetent patients with chronic hepatitis B famciclovir (11–13) and lamivudine (14–16) significantly decreased serum levels of HBV DNA, and produced sustained normalisation of alanine transaminase (ALT). Some hepatic histological improvement has also been observed (14–16).

A number of preliminary reports have described the efficacy of lamivudine (17–20) and famciclovir (21–25) in the prevention and treatment of recurrent and *de novo* hepatitis B infection in patients after liver transplantation. These studies indicated the potential for nucleoside analogues to treat or prevent hepatitis B infection following OLT; however, the numbers of patients studied were small (typically <20 per report), and therapy was continued for up to a maximum of only 2.5 years. In this observational study, famciclovir was made available on a compassionate-use basis for the treatment of hepatitis B infection in severely ill patients who had undergone OLT and subsequently had detectable serum HBV DNA. We report the efficacy and safety of treatment with famciclovir for up to 5 years in these patients.

Patients and methods

This open, compassionate-use programme included 130 patients with post-OLT hepatitis B infection, enrolled in 33 centres throughout Europe, Australia and Canada between March 1993 and August 1997. The study was approved by the local ethics review committee for each centre and all patients gave written informed consent in accordance with the Declaration of Helsinki and subsequent amendments. The dosage regimen of famciclovir was 500 mg tid, adjusted in patients with renal impairment such that those with a creatinine clearance of 30–59 mL/min/1.73 m^2 were administered famciclovir 500 mg bid and patients with a creatinine clearance of 10–29 mL/min/1.73 m^2 received one daily dose of 500 mg famciclovir.

The majority of patients (104) had recurrent hepatitis B infection, whereas 26 patients had either documented or presumed *de novo* or primary HBV infection. For the latter patients, HBV had either been acquired from the donor liver, had been present as subclinical infection prior to transplantation or was acquired *de novo* from an unknown source. Available data showed that at least 7/130 (5.4%) of all patients had received HBIG after transplantation, prior to administration of famciclovir. All patients receiving at least one dose of famciclovir (n=130) were assessed for safety; however, 50/130 patients were unassessable for ALT response to famciclovir treatment due to missing or unevaluable baseline data (29/130) or other reasons (21/130). A subgroup of 73 patients who had complete baseline data for both HBV DNA and ALT and who had been treated for at least 6 months were analysed for ALT response. Of the 57 patients not included in the 6 months' efficacy analyses, 30 had missing baseline HBV DNA and/or ALT data; 12 received treatment for less than 6 months; 9 were withdrawn and 6 terminally ill patients died within 6 months of starting famciclovir treatment. Three of the 73 patients were excluded from HBV DNA analysis since the actual value of their respective baseline HBV DNA measurements was not known, i.e. exceeded 2000 pg/mL; therefore, the percentage change in HBV DNA was not calculated for these three patients. These three patients were included in the analysis of ALT. The demographic data for all patients (n=130) and those evaluable for ALT, including 70 patients evaluable for HBV DNA response, were similar (Table 1).

Efficacy and safety parameters were measured and assessed at local centers. These parameters included HBV markers (HBV DNA, HBsAg, HBsAb, HBeAg and HBeAb), biochemical and haematological parameters in serum, and the recording of adverse events. All safety and efficacy parameters were to be assessed weekly for the first 4 weeks of famciclovir treatment and monthly thereafter for changes in serum levels of HBV DNA, ALT, serological response

Demographic data for the efficacy and safety of patient populations

Parameters	Safety population (all patients; *n*=130)	Efficacy population (6-month subgroup; *n*=73)
Age (years), median (range)	48 (12–71)	47.5 (23–71)
Gender, male/female (%)	106/24 (82%/18%)	58/15 (79%/21%)
Time from liver transplant to diagnosis (weeks), median (range)	29 (0–302)[a]	28 (0.6–302)
Time from diagnosis to famciclovir treatment (weeks), median (range)	42 (1.3–534)[a]	42 (1.3–534)
Patients with baseline HBV DNA[b] recorded, *n* (%)	107 (82%)	73 (100%)[c]
Patients with baseline ALT recorded, *n* (%)	116 (89%)	73 (100%)
Baseline ALT levels, median×ULN[d] (range×ULN[c])	2.9 (within range–94)	3.0 (within range–94)
Baseline serology, *n* (%)	74 (57%)	43 (59%)
HBeAg positive, HBeAb negative	50/74 (68%)	29/43 (67%)
HBeAg negative, HBeAb positive	18/74 (24%)	13/43 (30%)
Co-infection, *n* (%)		
Hepatitis C	11/130 (9%)	8/73 (11%)
Hepatitis D	10/130 (8%)	7/73 (10%)
Pre-treatment biopsy results, *n* (%)	117 (90%)	63 (86%)
Cirrhosis	15/117 (13%)	8/63 (13%)
Chronic active/persistent hepatitis	66/117 (56%)	36/63 (57%)
Hepatitis recurrence+other pathology[e]	36/117 (31%)	19/63 (30%)

[a] Information available for 129/130 patients.
[b] All of the patients assessed had active viral replication at the start of treatment, but different methods were used to measure serum HBV DNA levels (Genostics assay, Abbott, Illinois, USA; Murex; Digene, Maryland, USA; solid-phase hybridisation; or, branched-chain assay, Chiron Corp, California, USA), so the median HBV DNA could not be determined and is therefore not described.
c Three patients were excluded from the assessment of HBV DNA response since precise values for quantitative HBV DNA were not available for these patients.
[d] ULN, upper limit of normal.
[e] The most frequent 'other pathologies' were biliary dysfunction and rejection. Two of the patients with biliary dysfunction in both populations had a diagnosis of fibrosing cholestatic hepatitis.

Table 1

and signs and symptoms of the disease; however, the timings for these assessments varied for individual patients. A number of different quantitative methods were used to measure HBV DNA levels, based on availability at individual centres.

Responders were defined retrospectively, based on all available data, as patients who experienced a 70% or more decrease in HBV DNA levels from baseline, or who became HBV DNA negative, for at least two consecutive visits. This degree of reduction was consistent with criteria defining antiviral effects for antiviral agents used to treat HIV infection (21). Breakthrough recurrences were defined as responders who subsequently experienced a ≥3-fold increase in HBV DNA levels while still receiving famciclovir.

Efficacy analyses included calculation of median percentage reductions in HBV DNA and ALT, the proportion of patients who became HBV DNA negative, time to becoming HBV DNA negative and time to normalisation of ALT. Additionally, the effects of various parameters, i.e. baseline ALT levels, time from transplantation to infection, and time from HBV infection to treatment, were explored to assess their potential impact on treatment response. Although most patients had liver biopsies obtained prior to treatment with famciclovir, due to the compassionate use nature of the study no further liver biopsies were planned whilst the patients were on treatment or after treatment had been completed.

Results

Reduction in hepatitis B virus DNA levels in serum

Seventy-three patients received famciclovir treatment for at least 6 months and had a baseline HBV DNA recorded. Seventy of these patients had quantitative HBV DNA levels that allowed assessment of response to famciclovir treatment. Fifty-two (74%) of these 70 patients were classified as responders and 18 (26%) as non-responders. The baseline characteristics, i.e. HBV DNA, ALT and HBeAg status for responders and non-responders, were similar as

Baseline characteristics of responders and non-responders *Table 2*

Parameter		Responders (n=52)	Non-responders (n=18)
Baseline ALT (U/L), median (range)		107 (12–1950)	83 (11–2057)
Baseline ALT (U/L), median×ULN (range×ULN)		3.1 (within range–85)	2.8 (within range–94)
Baseline serology data			
HBeAg positive, HBeAb negative	n=29	19	10
HBeAg negative, HBeAb positive	n=13	12	1
HBeAg negative, HBeAb negative	n=2	2	0
Not available	n=26	19	7

is shown in Table 2. The median changes from baseline in HBV DNA levels for the responders are shown in Fig. 1.

Famciclovir treatment responders experienced a median reduction in HBV DNA levels of 91% after 12 weeks treatment (n=43). The median HBV DNA levels in famciclovir responders were reduced further to 95% among these patients who had received 6 months of treatment (n=48) and to >99% in responding patients who had received 18 months of treatment (n=15). In contrast to responders, in famciclovir non-responders, the initial median percentage decrease in HBV DNA, −23%, after 12 weeks of treatment (n=17), was followed by an increase in serum HBV DNA levels above baseline levels by 18 months (n=5) (data not shown). A clear difference between responders and non-responders was apparent by the rapid reduction of HBV DNA levels soon after the onset of famciclovir treatment (Fig. 2). Responders became HBV DNA-negative at the following timepoints: 20/52 (39%) after 6 months of famciclovir treatment, 8/17 (47%) after 2 years.

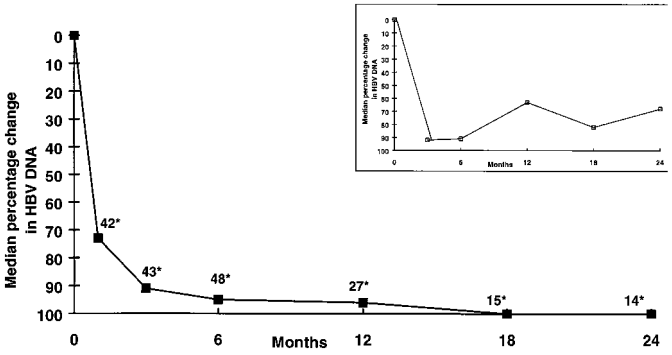

Fig. 1. **Changes from baseline for HBV DNA levels in responders to famciclovir treatment.** * Number of patients contributing data at each time point. Insert shows change in HBV DNA levels for responders with breakthrough (n=4).

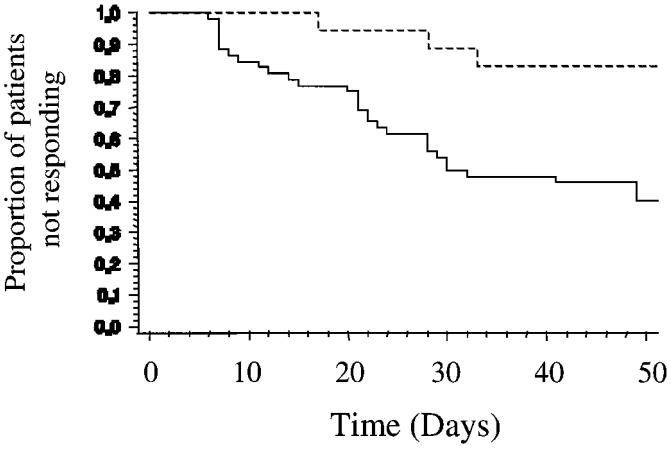

Fig. 2. **Kaplan–Meier plots for the time to HBV DNA response for responders (—) and non-responders (---) to famciclovir treatment.**

Alanine aminotransferase response

The magnitude of reductions in serum ALT levels were generally similar for responders and non-responders who had received at least 6 months of famciclovir treatment. There was no statistically significant difference between these groups for time to normalisation of ALT (hazard ratio of non-responders to responders=1.2, P-value=0.5). For patients with baseline ALT greater than three times the upper limit of normal range, a 72% median reduction in ALT was seen by 6 months in the responder group, whereas a 49% median reduction was seen in non-responders at the same timepoint. Further median reductions were seen in responder (81%) and non-responder (70%) groups with elevated baseline ALT after 12 months of famciclovir treatment. Also for patients with high baseline ALT, a similar proportion of responders and non-responders had normalised ALT levels after 6 months' treatment with famciclovir (16/51, 31% and 5/17, 29% respectively), increasing to 9/17 (53%) responders and 3/4 (75%) non-responders after 2 years of famciclovir treatment.

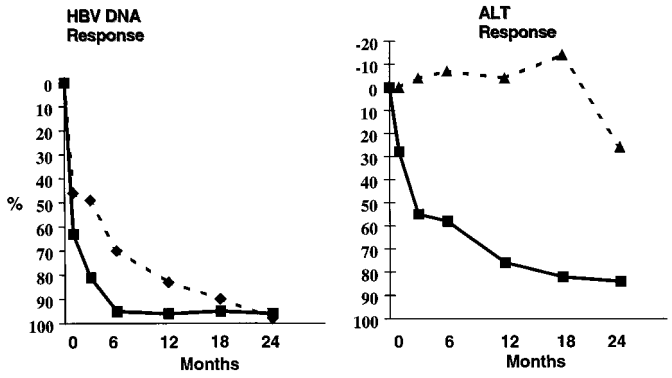

Fig. 3. **Comparison of HBV DNA and ALT response for patients with ALT ≥3×ULN (—) or ≤3×ULN (---) at the start of famciclovir treatment (median percentage reduction).**

Anti-HBe and anti-HBs seroconversion

Of the 43 patients with available HBe antigen and anti-HBe antibody data at baseline; 29 were HBeAg positive, anti-HBeAb negative. Nineteen (66%) of these patients were responders and 10 (34%) were non-responders. Of the HBeAg positive and HBeAb negative patients, 4 (14%) seroconverted, i.e. became HBeAg negative and anti-HBeAb positive, after 1, 6, 30 and 36 months of famciclovir treatment. Thirteen of 43 patients were HBeAg-negative, anti-HBeAb positive with active HBV replication at baseline. A larger proportion of these patients (92%, $n=12$) responded to famciclovir compared with patients who were HBeAg positive, HBeAb negative (19/29, 66%) at the start of famciclovir treatment. Three patients became negative for hepatitis B surface antigen (HBsAg) and anti-HBsAb positive after being treated with famciclovir for 1 (2 patients) and 6 months.

Predictors of famciclovir treatment response

Patients with high baseline ALT levels (≥3×ULN) experienced a statistically significantly greater percentage reduction in ALT levels (95% CI: −90%, −39%), and HBV DNA levels (95% CI: −44%, 0%), compared with patients with lower baseline ALT levels (<3×ULN) (Fig. 3). There were no other factors that were predictive of famciclovir treatment response.

Duration of treatment

As of February 1998, 72 patients had continued to receive famciclovir. At that time, 84 patients had received >6 months of famciclovir treatment, 41 had received >12 months of therapy, 20 patients had been treated for at least 2 years, 9 patients for >3 years, including 2 patients who had received treatment for nearly 5 years. Of the total of 130 patients, 58 had discontinued treatment. Four of these patients (3%) experienced a complete or satisfactory response, 37 (28%) were withdrawn due to lack of efficacy, 5 (4%) were withdrawn due to adverse events, one was withdrawn due to lack of available study medication and 11 patients (8.5%) died. For the 37 patients withdrawn due to lack of efficacy, the median duration of famciclovir treatment was 8 months (range <1 month to 4 years).

Safety

In general, famciclovir was well tolerated in this immunocompromised patient population with hepatitis B infection post-transplant. The most frequently reported non-serious adverse events in >5% patients were diarrhoea, 10% (13/130); headache, 7% (9/130); hepatitis, enzyme abnormality, leucopenia, asthenia and fatigue, each reported by 6% (8/130) of patients; and abnormal renal function, nausea and jaundice, each reported in 5% (7/130) of patients. The instances of hepatitis were considered to be as a result of the

Summary of non-fatal serious adverse events occurring in more than one patient, by WHO preferred term

WHO preferred term	Number of patients with event (%)
Total number of patients	130
Total number of patients with events	32 (24.6%)
Sepsis	4 (3.0%)
Confusion	3 (2.3%)
Hepatic failure	3 (2.3%)
Decreased therapeutic response	2 (1.5%)
Convulsions	2 (1.5%)
Encephalopathy	2 (1.5%)
Vomiting	2 (1.5%)
Ascites	2 (1.5%)
Abnormal hepatic function	2 (1.5%)
Cholestatic hepatitis	2 (1.5%)
Gallbladder disorder	2 (1.5%)
Diabetes mellitus	2 (1.5%)
Pancreatitis	2 (1.5%)
Haemorrhage	2 (1.5%)
Thrombocytopenia	2 (1.5%)
Pleural effusion	2 (1.5%)
Abnormal renal function	2 (1.5%)
Acute renal insufficiency	2 (1.5%)

Table 3

normal progression of the disease, and were not associated with hepatic flares.

Serious adverse events (SAEs) were reported infrequently for this patient population (32/130 patients: 25%, Table 3). None of the SAEs was considered by the investigator to be definitely related to treatment with famciclovir; 5 patients experienced SAEs that were considered possibly related to treatment. No patient developed fibrosing cholestatic hepatitis while on famciclovir treatment. Eleven patients (11/130, 8.5%) died following serious adverse events. The majority of deaths occurred early in the study (1994–1995), in patients who were already terminally ill on entry to the study and for whom there was no suitable alternative treatment. All of the deaths were associated with the patients' severe, refractory underlying condition. Six deaths were due to liver failure and the following resulted in one death each: circulatory failure, multi-organ failure, cardiac arrest, bleeding oesophageal varices and cardiogenic shock secondary to sepsis. No deaths were attributed to famciclovir treatment.

Of the 52 responders to famciclovir treatment, 4 patients experienced a breakthrough increase of HBV DNA levels: one following 6 months therapy, one following 12 months therapy and two following 18 months therapy with famciclovir. Median HBV DNA levels for these 4 patients remained significantly decreased compared with baseline. Patients with breakthrough recurrences continued to receive famciclovir treatment for 4, 9, 12, and 14 months, respectively, after the breakthrough had occurred. Two of these patients were subsequently treated with lamivudine.

Discussion

In 1994, Böker et al. (21) reported the first case of famciclovir treatment of hepatitis B infection post-OLT in a patient with fulminant recurrent hepatitis B infection post-OLT. Today, over 6 years later, the patient is extremely well and continues to receive famciclovir treatment. The initial promising reports of favourable famciclovir treatment response in liver transplant recipients have now been expanded to include many immunocompetent patients with chronic hepatitis B (11–13).

In the cohort reported here, three times as many treated patients responded to famciclovir treatment compared with non-responders. Among responders to famciclovir treatment, baseline HBV DNA levels were reduced by a median of 73% within 30 days of starting treatment with famciclovir, and further reduced to >90% within 12 weeks of starting therapy. The proportion of patients who became HBV DNA negative was similar to that reported in a phase II dose ranging famciclovir study (11). Patients with high (≥3×ULN) baseline ALT levels showed greater median percent reductions in serum levels of ALT and HBV DNA during famciclovir treatment. This was consistent with data reported for lamivudine treatment of patients with chronic hepatitis B (14).

In patients with active HBV DNA replication who were HBeAg negative and HBeAb positive at baseline, >90% responded favourably to famciclovir treatment. This may reflect the generally low HBV DNA levels observed in these patients. There were insufficient data provided to allow comparison of famciclovir treatment response for patients with recurrent hepatitis B infection with patients with documented or suspected *de novo* hepatitis B infection. A small percentage of patients did not respond to famciclovir treatment, and the reasons for the lack of response are unknown. Perhaps surprisingly, the reduction of ALT levels was similar in both responder and non-responder patients; however, changes in levels of immunosuppression could have contributed to the decrease in ALT; alternatively, the progression of recurrent hepatitis B infection post-transplant may follow a similar course as acute viral hepatitis with decline in ALT over time. The baseline characteristics, i.e., HBV DNA levels, ALT levels, timing of reinfection from date of transplantation, timing of reinfection post-OLT to start of famciclovir treatment, were comparable for responders and non-responders. To date, there are no data that suggest differences in famciclovir pharmacokinetics based on demographic or genetic differences.

Famciclovir was well tolerated in patients treated for up to 5 years, with a relatively low frequency of serious adverse events. There was no evidence of the toxicity problems seen with fialuridine that caused inhibition of mitochondrial function (26). A small number of patients (5%) developed breakthroughs in which HBV DNA levels became positive after previously being suppressed. Breakthroughs have been previously reported for patients treated with lamivudine (27–30) and, less frequently, for famciclovir (31). Variants selected on lamivudine therapy show a high level of resistance, which is associated with either a methionine-to-valine or methionine-to-isoleucine substitution in the highly conserved tyrosine-methionine-aspartate-aspartate (YMDD) locus within the catalytic site (domain C) of HBV polymerase (27–29). To date, no mutations in the YMDD locus have been detected during famciclovir treatment. In contrast, variants of HBV selected during therapy with famciclovir have contained mutations in domain B (the template binding site) of HBV polymerase which were associated with only 3-fold reductions in susceptibility to penciclovir. In addition, these isolates were not cross-resistant to lamivudine and the time taken to develop resistance was slow (32).

The open compassionate-use nature of this study inherently leads to some measure of variability in the data collected (e.g. multiple methodologies for HBV DNA determination, variation in

extent of patient follow-up). This variability resulted in the retrospective determination of famciclovir response, as it was not possible to define treatment success prospectively when use of several methods for HBV DNA quantification was permitted. Nevertheless, effective HBV DNA suppression was documented in at least a substantial subgroup of this, the largest group of famciclovir treated patients with HBV infection or recurrence following liver transplantation described to date.

Lamivudine has been shown to be more potent than famciclovir in suppression of HBV DNA replication (33) and has shown promise in the treatment of hepatitis B reinfection in liver transplant recipients (18, 19). Consequently, lamivudine is considered appropriate first-line therapy for recurrent hepatitis B after liver transplantation. However, due to the development of mutations and the associated viral resistance, particularly in immunocompromised patients, combination treatment with several nucleoside analogues is likely to be the way forward. Famciclovir certainly deserves consideration as a candidate for such combination treatment.

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