Outcome of renal transplantation in hepatitis B surface antigen-positive patients after introduction of lamivudine

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Abstract

Background. In end-stage renal disease patients with hepatitis B surface antigen (HBsAg), the risk of hepatic dysfunction after immunosuppression represents a large barrier in renal transplantation. Lamivudine is a potent inhibitor of hepatitis B virus (HBV) replication. We retrospectively investigated the outcome of HBsAg-positive renal transplantation recipients after lamivudine had become available.

Methods. From July 1994 to August 2000, seventeen HBsAg-positive patients (M : F = 15 : 2) received renal allografts (13 : 4 living : cadaveric donors). Liver function tests at the time of transplantation were normal in all patients. Pre-transplant liver biopsies performed in 15 patients demonstrated minimal inflammatory histology, except in three patients showing pathological and clinical signs of active hepatitis. Lamivudine was started pre-operatively in these three subjects. Another seven patients were treated with lamivudine for post-operative hepatic dysfunction. The remaining seven patients did not develop hepatic dysfunction after transplantation.

Results. Lamivudine was initially effective in decreasing serum HBV DNA titres, and in normalizing hepatic enzymes. Lamivudine was well tolerated without significant side effects for 35.5 ± 8.9 months after initiation of treatment. HBV DNA became negative in nine patients but remained positive in one patient. Among the nine patients with initial negative conversion of HBV DNA, two developed transient positive conversion of HBV DNA and two demonstrated persistent positive conversion. Among the patients with normal liver histology in the pre-transplant period, 41.6% (5/12) developed liver pathology progression after immunosuppression. All 17 patients had functioning grafts, except for one patient who developed relapsed IgA nephropathy.

Conclusions. Our data showed relatively favourable outcomes in hepatitis B-positive renal transplant recipients receiving lamivudine treatment, even though two patients developed lamivudine resistance.

Keywords: hepatitis B; lamivudine; liver biopsy; prognosis; renal transplantation

Introduction

In hepatitis B surface antigen (HBsAg)-positive renal transplant recipients, the use of immunosuppression may allow the rapid replication of hepatitis B virus (HBV), resulting in severe hepatitis. When pre-transplantation work-up reveals HBsAg in patient serum, the decision to perform kidney transplantation should be made with great care. To identify patients who are likely to suffer from progressive life-threatening hepatitis after kidney transplantation, liver biopsies are recommended in patients with hepatitis B infection [1]. If the biopsy shows severe hepatitis or cirrhosis, kidney transplantation is not recommended, however, in the case of mild hepatitis kidney transplantation is usually permitted [2]. Nevertheless, there is still a significant risk of liver failure after kidney transplantation in mild hepatitis patients. Higher mortality from chronic liver disease has been reported even in patients having the chronic asymptomatic hepatitis B carrier state after kidney transplantation [3,4].

Antiviral therapies such as adenine arabinoside, acyclovir, and interferon-α have been used to treat chronic hepatitis B [5]. To date, interferon-α may represent the best treatment option for the management of chronic hepatitis B. However, this treatment may not be safe in the setting of kidney transplantation because interferon-α therapy has been reported to cause deterioration of graft function [5,6].

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Lamivudine, the (−) enantiomer of 3’-thiacytidine, is a potent inhibitor of HBV replication in patients with chronic HBV infection [7]. Successful results of lamivudine trials examining advanced and decompensated liver disease or recurring chronic hepatitis B after liver transplantation have been reported [7,8]. Lamivudine was also a safe and effective therapy for activated hepatitis B in renal transplant recipients in short-term follow-up [9–11]. It is likely that lamivudine therapy may produce more favourable outcomes for renal graft recipients with HBsAg.

In this study, we retrospectively investigated the outcome of renal graft recipients with HBsAg after lamivudine had become available. We also evaluated the usefulness of pre-transplant liver biopsy and serological viral markers, such as HBV DNA and HBeAg, in predicting the risk of liver dysfunction after renal transplantation.

Subjects and methods

Some 839 renal transplantations were performed in our centre between July 1994 and August 2000 (living: 557, cadaver: 282). Of these, 17 patients (15 males and 2 females), with a mean age of 32.8 ± 10.6 years (range: 16–56 years), were HBsAg-positive at the time of transplantation. Liver biopsy, performed pre-operatively in 15 patients, revealed active inflammatory changes, such as limiting plate necrosis and/or periportal fibrosis in 3 patients and normal to minimal inflammation in the remaining 12 patients. Two patients refused liver biopsy before transplantation. For the three patients having active inflammatory hepatitis in pre-transplant liver biopsies, lamivudine was started before transplantation (group I). The kidney transplantations were performed 2–8 months later, when donors were available and liver enzymes became normal. For the remaining 14 patients, including the two patients that refused liver biopsy, operations were performed without lamivudine because alanine aminotransferase (ALT) levels were normal and liver biopsies showed only a few portal inflammations and no lobular necrosis or fibrosis (Ludwig criteria: grade/stage = 0 or 1/1) [12] (group II). After transplantation, seven of 14 patients had maintained normal ALT levels for the entire study period (group IIa), whereas the other seven patients developed ALT elevations. Lamivudine therapy was begun for those seven patients after biopsy (group IIb).

Thirteen patients received renal grafts from living related donors who were HBsAg-negative. The remaining four patients received renal grafts from HBsAg-positive cadaveric donors, which would have been abandoned if the patients and their families had not accepted the grafts. All patients were treated with cyclosporine A based triple immunosuppressants.

In our centre, the immunosuppressive protocol includes an initial maintenance of cyclosporine A trough levels at 250–350 ng/ml (radioimmunoassay, Cyclo-Trac® SP-Whole blood, Diasorin, Monesota) up to 2 months post-operatively, followed by 200–250 ng/ml during post-operative months 2 through 6. After 6 months, cyclosporine A levels were maintained at 150–200 ng/ml for 1 year post-operatively, and thereafter were maintained at 100–150 ng/ml. Methylprednisone was given 500 mg intravenously during the operation and was then tapered by 2.5–5.0 mg daily, from an initial 60 mg/day to 20 mg/day. Thereafter, prednisone was tapered more slowly. Azathioprine was given 50–75 mg/day and was adjusted according to white blood cell count. In certain cases who developed hepatic dysfunction, cyclophosphamide was temporarily substituted for azathioprine. Monoclonal and polyclonal antibodies were not used for prophylactic therapy or antirejection therapy. Detailed clinical features are shown in Table 1.

Viral markers and hepatic enzymes

Serum HBsAg was measured by radioimmunoassay (Abbott Diagnostics, North Chicago, IL, USA), and HBeAg by a commercially available immunoradiometric assay kit (Sorin Biomedica, Saluggia, Italy). HBV DNA was measured using a molecular hybridization technique (Abbott Diagnostics, North Chicago, IL) with a detection limit of 1.5 pg/ml. Serum chemistries, including liver function tests, were routinely performed once a month. ALT was measured using an autoanalyser (747-200 autoanalyser; Hitachi® Tokyo, Japan). ALT levels up to 40 IU/l were considered normal. Hepatitis C antibody and hepatitis D antibody levels were negative in all patients.

Liver biopsy

Hepatic pathology was scored by grade and stage, according to the method of Ludwig [12].

Statistics

Data are expressed as means ± SD. Non-parametric tests (Wilcoxon signed rank test or Wilcoxon rank sum test and Fisher’s exact test) were used to compare the values. Comparisons were considered statistically significant at P < 0.05.

Results

Group I

In this group, pre-transplant liver biopsy showed mild to moderate limiting plate necrosis with lobular features are shown in Table 1.

Table 1. Clinical characteristics of patients

<table>
<thead>
<tr>
<th>HBsAg-positive patients (n = 17)</th>
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</thead>
<tbody>
<tr>
<td>Mean age (years), (range)</td>
</tr>
<tr>
<td>Sex (M: F)</td>
</tr>
<tr>
<td>Donor (living: cadaver)</td>
</tr>
<tr>
<td>History of dialysis</td>
</tr>
<tr>
<td>Haemodialysis: CAPD</td>
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<tr>
<td>Mean duration of dialysis (months), (range)</td>
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<tr>
<td>Primary renal disease</td>
</tr>
<tr>
<td>Chronic glomerulonephritis (GN)</td>
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<tr>
<td>IgA nephropathy</td>
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<tr>
<td>Hepatitis B-associated GN</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Alport’s syndrome</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
</tr>
<tr>
<td>Unknown</td>
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</tbody>
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necrosis and periportal or portal to portal fibrosis (Table 2). All three patients were HBV DNA-positive (6.1, 35.9, 11.3 pg/ml) and ALT levels were high. Lamivudine was started at 25–100 mg/day for 2–8 months pre-operatively. HBV DNA rapidly disappeared within 1–2 months following lamivudine therapy. Transplantations were performed when the donors were available and when ALT levels were normal. After the operation, the lamivudine dose was increased to 100–150 mg/day. However, in patient 1, HBV DNA became positive at 19 months in spite of continuous lamivudine therapy, and the titres were at 223 pg/ml by the end of follow-up (48 months after therapy). Although ALT levels increased with positive conversion of HBV DNA in patient 1, they have remained stable thereafter (68 IU/l at post-operative 40 months).

**Group II**

Fourteen patients were included in this group. Among these, seven patients maintained normal ALT levels up to the last follow-up (42.8 ± 13.4 months, range: 18–62 months, group IIa) (Table 3), but the remaining seven developed biochemical signs of hepatic dysfunction during follow-up (49.5 ± 17.3 months, range: 29–74 months, group IIb) (Table 4). There was no difference in follow-up duration between groups IIa and IIb.

In group IIa, the marker of HBeAg and HBeAb did not change during follow-up (Table 3). However, the titre of HBV DNA increased after immunosuppression. Interestingly, five patients showed positive HBeAg and HBV DNA along with normal ALT for the entire study period. This was especially true for patient 4, and liver biopsy was performed again at post-operative month 35. The second liver biopsy did not show any histological progression (grade/stage: 0/1).

In group IIb, HBV DNA was positive in all patients with deterioration of liver function. The titre of HBV DNA ranged from 72.5 pg/ml to >4000 pg/ml (Table 4). Four of seven patients were pre-core mutants (patients 11, 12, 13, 17). Post-transplant liver biopsies showed progressive changes in all patients. Mild to severe limiting plate necrosis and bridging necrosis were found, as well as periportal or septal fibrosis (Table 4). Lamivudine was started at 100–150 mg/day 6–31 months post-operatively. By three months after therapy, ALT levels decreased significantly from 147 ± 103 to 34.7 ± 6.9 IU/l ($P < 0.05$), and at the end of follow-up, ALT was 47 ± 59 IU/l in these seven patients. HBV DNA was undetectable 1–8 months later, except in one patient (patient 11) having a DNA titre that decreased from 1760 pg/ml to 4 pg/ml at 3 months after therapy. At the last follow-up, the titre increased to 139 pg/ml. After a negative conversion in patient 13, HBV DNA reappeared at 9 months after therapy due to non-compliance and his renal function declined to dialysis level because of biopsy confirmed-relapsed IgA nephropathy. Until haemodialysis, HBV DNA was persistently positive with elevations in ALT. In two other patients (patients 14, 15), HBV DNA became transiently positive due to non-compliance, but was restored to negative levels at 2 and 8 months after restarted lamivudine therapy. Lamivudine was well tolerated in all patients without significant side-effects during follow-up.

**Renal functions in 17 patients**

Four episodes of acute rejection were observed in three patients and they were treated with steroid pulse therapy. Among our seventeen patients, only one lost his graft because of relapsed IgA nephropathy and the remaining 16 patients maintained functioning grafts in the follow-up period of 44.2 ± 14.5 months (range: 18–74 months). The mean serum creatinine of the 16 patients was 1.3 ± 0.4 mg/dl (range: 0.7–2.3 mg/dl). No patient died during follow-up.

**Viral markers and liver histology**

For the entire study period, HBsAg was persistently positive in 17 patients. Lamivudine therapy had no effect on the negative conversion of HBsAg. Four patients (patients 1, 6, 7, 15) received grafts from HBsAg-positive cadaveric donors and they were included in groups I, IIa, and IIb.

In cases of deteriorating liver function, HBV DNA was positive in each patient (10/10), and HBeAg was positive in 5/10 patients. These results were the same when compared with patients having normal ALT.

<table>
<thead>
<tr>
<th>Sex/age</th>
<th>At the time of lamivudine treatment</th>
<th>Last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eAg/DNA (pg/ml)</td>
<td>Pathology (grade/stage)</td>
</tr>
<tr>
<td>1. M 35,6</td>
<td>+/6.1</td>
<td>2/1</td>
</tr>
<tr>
<td>2. M 26</td>
<td>+/35.9</td>
<td>1/2</td>
</tr>
<tr>
<td>3. M 36</td>
<td>–/11.3</td>
<td>3/2</td>
</tr>
</tbody>
</table>

*Months.  
This patient developed lamivudine resistance after 19 months of lamivudine use despite continuous therapy.
Among the 12 patients having normal to minimal inflammatory pre-transplant liver biopsies, five (patients 11, 12, 13, 14, 17) developed an aggravation of liver pathology at 6–23 months post-operatively. Pre-operative histology revealed positive HBsAg in 8/11 patients and positive HBeAg in 5/11 patients. Unfortunately, HBsAg and HbcAg were not available in one patient. In post-operative liver biopsies from the latter five patients, all showed positive HBsAg and HBeAg. When lamivudine was not given, fibrosing cholestatic hepatitis (grade/stage: 2/2) was found at 8 months post-operatively (patient 12), and liver cirrhosis (grade/stage: 4/4) was found at 23 months post-operatively (patient 17) despite a near normal pre-operative histology. In patient 15, a post-operative second liver biopsy showed fibrosing cholestatic hepatitis (grade/stage: 4/3), and diminishing liver function because of non-compliance. Interestingly, acute rejection developed post-operatively in patients 12 and 15. In these three patients, liver function stabilized and DNA was converted to negative after lamivudine therapy. Figures 1 and 2 show the clinical course of patients 12 and 15 with developing fibrosing cholestatic hepatitis.

### Discussion

The safety and efficacy of renal transplantation in HBsAg-positive patients has been debated for almost two decades [13]. In a case-control study by Mathurin et al. [4], both 10-year graft and patient survival were significantly lower in HBV-infected patients. In a natural history study, 151 HBsAg-positive kidney transplant recipients developed a high rate of histological deterioration (85.3%), accompanied by cirrhosis and hepatocellular carcinoma [14]. In the study by Parfrey et al. [3], about 60% of HBsAg-positive patients progressed to chronic active hepatitis or cirrhosis after renal transplantation, and 50% of them died from active hepatitis.

In the present study, we experienced a similar incidence of liver disease progression: seven out of 14 HBsAg-positive patients developed clinical and pathological signs of active hepatic dysfunction. This occurred even though they showed normal to minimal inflammatory histology and/or normal liver function at the time of transplantation. These results suggest that HBsAg-positive renal transplant recipients have a significant risk of developing hepatic dysfunction. However, lamivudine treatment effectively controlled hepatic inflammation in the 7 HBsAg-positive patients.
Fig. 1. The clinical course of patient 12. Pre-transplant liver biopsy showed near normal histology (grade: stage: 1/1). However, when ALT levels increased along with positive conversion of HBV DNA, post-transplant liver biopsy showed fibrosing cholestatic hepatitis (grade: stage: 2/2). After lamivudine therapy, ALT levels stabilized and HBV DNA became negative.

Fig. 2. The clinical course of patient 15. ALT levels increased at 12 months post-operatively. Lamivudine was started after liver biopsy showed active inflammatory hepatitis (grade: stage: 3/2). Following lamivudine treatment, ALT levels decreased. However, after a brief period of non-compliance, ALT levels increased and a second liver biopsy demonstrated additional pathology (grade: stage: 4/3, fibrosing cholestatic hepatitis). Lamivudine was reintroduced, and, fortunately, ALT levels stabilized along with negative conversion of HBV DNA.
rebound. Although we did not perform genotype resistance to lamivudine, and another two non-
vudine resistance would be optimal for these patients. In the present study, HBV DNA was persistently positive after 6 months of therapy. In the present study, HBV DNA titres decreased in one patient from 1760 pg/ml to 4 pg/ml after therapy, however, it gradually increased to 139 pg/ml at the last follow-up.

The presence of HBV DNA, HBeAg, or both prior to transplantation has been thought to be associated with increased mortality from liver disease [15]. However, in our study, among patients who maintained stable liver function part-operatively, nearly 70% of patients had positive pre-operative HBeAg and HBV DNA. Our data may, therefore, suggest that HBeAg and HBV DNA have no relationship to the later development or aggravation of hepatitis. These results are similar to those of Huang et al. [16], showing that the presence of HBV DNA did not correlate with the later development of chronic hepatitis. Both CD4+ and CD8+ T cell responses to viral antigens are important factors for hepatocyte damage caused by HBV [17]. The balance between helper T cells and cytotoxic T cells may be crucial for the regulation of liver injury and viral clearance. The important mechanism of hepatic cell damage involves the T cell response, and not merely the presence of replicating viral markers.

Rao et al. [1] argued that histological diagnosis may be a useful marker for predicting the course of chronic liver disease after renal transplantation. In our study, among the 12 patients with near normal initial liver biopsy, five (41.6%) developed clinical and pathologic signs of progressive liver disease. Therefore, it is fair to state that normal to minimal inflammatory changes in pre-operative liver biopsy do not guarantee normal hepatic function after immunosuppression.

The emergence of HBV resistance to lamivudine remains a major concern during prolonged therapy [18,19]. A rebound in HBV DNA after initial suppression may be explained by non-compliance or lamivudine resistance [18]. In renal transplant recipients, the incidence of rebound was reported to be 15.7% or 30.8% [11,19]. The most resistant patients carried YMDD (tyrosine-methionine-aspartate-aspartate) mutations in viral replicate, which is the target of lamivudine. Therefore, a combination therapy including lamivudine plus another antiviral that prevents lamivudine resistance would be optimal for these patients. In the present study, HBV DNA was persistently positive in one patient. Two other patients developed resistance to lamivudine, and another two non-compliant patients developed a transient HBV DNA rebound. Although we did not perform genotype analysis, we believe that our population included YMDD mutations, a possibility that merits further investigation.

In the study by Dienstag et al. [7], HBV reactivation was observed in 71% of patients who discontinued lamivudine treatment. Fortunately, in the present study, liver function was relatively stable during continuous or resumed lamivudine therapy in patients with final rebound. Severe flare-up leading to fulminant hepatic failure, as reported by Peters et al. [20], was not observed in our study. Kletzmayr et al. [11] reported similar findings to our results. Although we postulate that HBV rebound does not always predict deteriorating liver function, larger prospective studies are needed to confirm this possibility.

Important issues regarding lamivudine introduction in renal transplant patients with HBsAg include whether the therapy should be started as prophylaxis or whether treatment should be continued on a lifelong basis.

In conclusion, careful pre-transplant evaluation of patients including liver biopsy and lamivudine therapy before or after transplantation may lead to favourable outcomes in HBsAg-positive renal transplant patients.

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