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LAMIVUDINE FOR THE TREATMENT OF HEPATITIS B VIRUS-RELATED LIVER DISEASE AFTER RENAL TRANSPLANTATION: META-ANALYSIS OF CLINICAL TRIALS

FABRIZIO FABRIZI,[1,4,5] GARETH DULAI,[2,3] VIVEK DIXIT,[2] SUPHAMAI BUNNAPRADIST,[1] AND PAUL MARTIN[1,2]

Background. **Numerous reports have appeared on lamivudine use for the treatment of hepatitis B virus (HBV) infection after renal transplantation (RT). However, the efficacy and safety of lamivudine after RT remain unclear.**

Methods. **The authors evaluated the efficacy and safety of initial lamivudine monotherapy in RT recipients with hepatitis B by performing a systematic review of the literature with a meta-analysis of clinical trials. The primary outcomes were hepatitis B (HB) e antigen (Ag) and HBV-DNA clearance (as measures of efficacy); the secondary outcomes were biochemical response (as measures of efficacy), dropout rate, and lamivudine resistance (as measures of tolerability). The authors used the random effects model of DerSimonian and Laird, and outcomes were analyzed on an intent-to-treat basis.**

Results. **The authors identified 14 clinical trials (184 patients); all of these were prospective cohort studies. The mean overall estimate for HBV-DNA and HBeAg clearance, alanine aminotransferase normalization, and lamivudine resistance was 91% (95% confidence interval [CI], 86%–96%), 27% (95% CI, 16%–39%), 81% (95% CI, 70%–92%), and 18% (95% CI, 10%–37%), respectively. HBeAg seroconversion rate was assessed in four (28%) trials and ranged between 0% and 46%. The *P* value was greater than 0.05 for our test of study homogeneity. There was no association between rate of patients who were male patients or had cirrhosis, race, age, lamivudine dose, and HBV-DNA or HBeAg clearance. Increased duration of lamivudine therapy was positively associated with frequency of HBeAg loss ($r=0.51$, $P=0.039$) and lamivudine resistance ($r=0.620$, $P=0.019$). Only 2 (14%) of 14 studies reported a dropout rate greater than 0%.**

Conclusions. **Our meta-analysis showed that the majority of RT recipients with hepatitis B had high virologic and biochemical response with lamivudine. Tolerance to lamivudine was good. However, lamivudine resistance was frequent with prolonged therapy, potentially limiting its long-term efficacy after RT.**

With the improving results of renal transplantation (RT), liver disease has emerged as an important cause of morbidity and mortality (*1*). It has been calculated that liver failure is the cause of death in 8% to 28% of long-term survivors after RT (*2*). Hepatitis B virus (HBV) infection remains an important cause of liver disease in RT recipients nearly 30 years after the Centers for Disease Control recommendations for its control within dialysis units. The reported prevalence of chronic hepatitis B (HB) surface (s) antigen (Ag)-positive carriers after RT varies from 10% to 25% in many centers (*1*, *3*).

Lamivudine has been approved for the treatment of chronic hepatitis B in immunocompetent patients. It is a potent inhibitor of HBV replication by competitive inhibition of viral reverse transcriptase and termination of proviral DNA chain extension (*3*). Large multicenter trials have established the efficacy and safety of lamivudine in the treatment of chronic hepatitis B in patients with normal renal function (*4–6*).

Information concerning the outcome of HBV infection after kidney transplantation had been a subject of controversy (*1*, *3*). Recent studies with extended periods of follow-up have emphasized the adverse consequences of HBV infection on long-term graft and patient survival after RT (*1*, *3*). HBV-related glomerulonephritis occurring after RT may further decrease graft survival (*1*). To date, several authors have reported the use of lamivudine for treatment of HBV-related liver disease after RT (*7–26*), although the efficacy of lamivudine in this population remains incompletely defined. The primary goal of this study was to synthesize the available evidence on the efficacy and safety of lamivudine therapy in RT recipients with HBV-related liver disease by performing a systematic review of the literature with a meta-analysis of clinical trials.

PATIENTS AND METHODS

Search Strategy and Data Extraction

Electronic searches of the National Library of Medicine's MEDLINE database, Current Contents, and manual searches of selected specialty journals were performed to identify all pertinent literature (*27*). The key words "hepatitis B," "lamivudine," and "renal transplantation" were used. Reference lists from qualitative topic reviews and published clinical trials were also searched. All English and non-English articles were identified by a search from 1990 through July 2002. Data extraction was conducted independently by two investigators (F.F. and V.D.), and consensus was achieved for all data. Studies were compared to eliminate duplicate reports for the same patients, which included contact with investigators when necessary. Eligibility and exclusion criteria were prespecified. This work was conducted at the Center for Liver and Kidney Diseases and Transplantation, Cedars-Sinai Medical Center and David Geffen

[1] Center for Liver and Kidney Diseases and Transplantation, Cedars-Sinai Medical Center, Los Angeles, CA.
[2] Division of Digestive Diseases, UCLA School of Medicine, Los Angeles, CA.
[3] GLAVA Healthcare System, Los Angeles, CA.
[4] Division of Nephrology and Dialysis, Maggiore Hospital, IRCCS, Milano, Italy.
[5] Address correspondence to: Fabrizio Fabrizi, M.D., Divisione di Nefrologia, Dialisi e Trapianto, Ospedale Maggiore, Policlinico IRCCS, Pad. Croff, via Commenda, 15 Milano, 20122 Italy. Email: fabrizi@policlinico.mi.it.

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School of Medicine, University of California at Los Angeles, Los Angeles, CA.

Criteria for Inclusion

To be included in this systematic review, a clinical trial had to fulfill a set of criteria. It had to be published as an article, report the results of primary lamivudine therapy, and use the clearance of HBV viremia (HBV-DNA), HBeAg, or both from serum as clinical endpoints. Studies that included patients on maintenance hemodialysis or peritoneal dialysis were excluded. The decision as to the inclusion or exclusion of clinical trials was not related to results.

Ineligible Studies

Studies were excluded if they reported inadequate data on treatment or measures of response, or included patients with coexisting diseases such as infection with human immunodeficiency virus, hemophilia, or other forms of liver disease such as hepatitis C, hepatitis A virus, Epstein-Barr virus, cytomegalovirus, Wilson's disease, hemochromatosis, α_1-antitrypsin deficiency, and alcoholic hepatitis-cirrhosis or autoimmune hepatitis, or complications such as hepatocellular carcinoma. Trials that were only published as abstracts or as interim reports were excluded. Trials that involved previously treated patients, nonresponders, or relapsers were excluded. We excluded patients with predialysis or dialysis-dependent renal insufficiency and those with nonfunctioning renal grafts.

Definitions

The primary measures of efficacy in this systematic review were HBeAg and HBV-DNA clearance after lamivudine therapy. HBV-DNA clearance was defined as the disappearance of HBV viremia from serum at the end of antiviral therapy. In all studies, HBV-DNA levels were measured by molecular hybridization techniques with a sensitivity limit ranging between 0.5 and 1.5 pg/mL (1.4×10^5 and 4.3×10^5 HBV-DNA copies/mL). The HBeAg clearance was defined as loss of detectable HBeAg from serum after completion of antiviral therapy.

Secondary endpoints included dropout rate, lamivudine resistance, and biochemical response. Dropout rate and lamivudine resistance were measures of tolerability; lamivudine resistance was defined by the reappearance of detectable HBV-DNA during lamivudine therapy in blood samples of patients whose HBV-DNA level had become repeatedly undetectable under lamivudine. Biochemical response was defined as the normalization of alanine aminotransferase (ALT) levels at the end of the treatment. These definitions were consistent with standards published in the literature. This meta-analysis was not supported by any pharmaceutical company.

Statistical Methods

Outcomes were analyzed on an intent-to-treat basis (i.e., all patients included in these studies were considered for the calculation of the response rate, and patients without the endpoint were considered as treatment failures). When not given in the publication, the response rate according to the intent-to-treat method was recalculated by the data abstractors (F.F. and V.D.). Quantitative, pooled, summary estimates of HBV-DNA, HBeAg clearance, and ALT normalization rates across individual studies were generated using the random effects model of DerSimonian and Laird (*28*). For the DerSimonian and Laird method, the hypothesis is that the studies are a random sample from a population of studies (random sample) (*28*). The mean of the population of studies is the "true effect." The random effects model incorporates the heterogeneity of the studies. The overall treatment effect is estimated by a weighted average of the individual effects, with weights inversely proportional to the variance of the observed effects. Ninety-five percent confidence intervals (CI) for point estimates were computed using nonparametric resampling (bootstrap) methods, each with 1,000 resamples. Chi-square test statistics were used to test for homogeneity across studies, and Spearman correlation coefficients were used to assess the association between outcomes of interest (e.g., the reported size of the estimated intervention benefit) and variables thought to be potential sources of heterogeneity (e.g., various subjects and trial characteristics of interest). A value of $P<0.05$ was considered to be statistically significant.

RESULTS

Literature Review

Our electronic and manual searches identified 20 articles that were selected for full text review (*7–26*). All 20 candidates studies were written in English. Six studies were excluded because they did not fulfill the inclusion criteria (*21–26*). The remaining 14 studies, representing a total of 184 unique patients, were included in our meta-analysis (*7–20*). There was a 100% concordance between reviewers with respect to final inclusion and exclusion of studies reviewed on the basis of the predefined inclusion and exclusion criteria.

Patient Characteristics

Some salient demographic and clinical characteristics of subjects enrolled in the included clinical trials are shown in Table 1. All trials were published in English from 1997 to 2002 and included RT recipients with HBV-related liver dis-

TABLE 1. Characteristics of clinical trials: demographic and clinical data[a]

Authors	Age (yr)	Country of origin	Men (%)	Time after RT (mo)
Rostaing et al., 1997[7]	49 ± 6	France	5 (83)	70 ± 49
Goffin et al., 1999[9]	52	Belgium	4 (100)	156
Jung et al., 1998[8]	35	Korea	6 (100)	8
Kletzmayr et al., 2000[15]	49 ± 12	Austria	15 (79)	119 ± 65
Tsai et al., 2000[14]	40.5 ± 7.5	Taiwan	6 (54)	NA
Lewandowska et al., 2000[11]	46.5	Poland	21 (75)	NA
Antoine et al., 2000[13]	50	France	9 (75)	132
Mouquet et al., 2000[12]	38 ± 9	France	NA	NA
Fontaine et al., 2000[10]	47	France	17 (65)	NA
Lee et al., 2001[18]	34.5 ± 15	Taiwan	11 (85)	30.9 ± 33
Han et al., 2001[16]	35.9	Korea	5 (83)	9.6 ± 5.7
Chan et al., 2002[20]	47 ± 12	Hong Kong	21 (81)	82 ± 58
Park et al., 2002[19]	30.3 ± 8.2	Korea	9 (90)	NA
Mosconi et al., 2001[17]	33 ± 17	Italy	3 (75)	NA

[a] Data expressed as mean ± SD.
NA, Not available.

ease undergoing therapy with lamivudine. The majority (8 of 14 [57%]) of studies were from centers in western Europe. The mean age of subject cohorts ranged from 30 to 52 years of age. The gender distribution ranged from 54% to 100% male. The mean time after RT before initiation of treatment varied from 8 to 156 months, although six studies did not report data on this characteristic.

The baseline virologic and biochemical status of patients is listed in Table 2. HBsAg, HBV-DNA status, and ALT were documented at study entry in all studies. Data on HBeAg and serum antibody to HBeAg (HBeAb) were available in 86% (12 of 14) and 36% (5 of 14) of reports, respectively. It seems that lamivudine therapy was given to HBsAg-positive RT recipients, the majority of whom had detectable HBV-DNA (162 of 186 [87%]) or elevated ALT (119 of 186 [64%]) in serum. Many patients were HBeAg-positive (102 of 171 [60%]) before lamivudine therapy.

Table 3 provides details of the study design, including dose and duration of lamivudine therapy in these prospective cohort studies. Serologic and virologic data on the efficacy of treatment are summarized in Table 4. HBeAg seroconversion, defined as the loss of HBeAg and HBV-DNA from serum and the appearance of antibodies against HBeAg, was assessed in four (28%) trials (*9–10*, *15*, *18*); the HBeAg seroconversion rate after antiviral therapy is shown in Table 4.

As shown in Table 5, data on histologic characteristics were not as well documented in most of these studies. On the basis of the data provided, however, it appears that the majority of enrolled subjects were noncirrhotics with HBV-related liver disease. Liver biopsy at the beginning and the end of lamivudine therapy was performed in only two trials (Table 5).

Summary Estimates of Outcome

The mean overall estimate for HBV-DNA clearance (n=14) was 91% (95% CI, 86%–96%). The *P* value was greater than 0.05 for our test of study homogeneity, suggesting that the selected studies were homogeneous with respect to the primary outcome endpoints. The mean overall estimate for HBeAg clearance (n=12) was 27% (95% CI, 16%–39%). The mean overall estimate for ALT normalization (n=9) was 81% (95% CI, 70%–92%).

Despite the apparent homogeneity of trials with respect to outcomes, we examined the relationship between outcomes and several sources of potential variation between trials. Outcomes from studies conducted in Asia (n=6) did not differ from those conducted outside of Asia (n=8) with respect to either mean±SD rates of HBV-DNA clearance (89±13% vs. 92±12%) or HBeAg clearance (31±22% vs. 23±28%). There were no apparent clinically or statistically significant associations between the proportion of study patients who were male patients or had cirrhosis, age, and the reported rates of HBV-DNA or HBeAg clearance, nor were there any discernible relationships between these measures of outcome and the dose of lamivudine. Interestingly, although the rate of HBV-DNA clearance was not associated with the duration of lamivudine therapy ($r=-0.009$, not significant), the rate of HBeAg clearance was positively associated with increasing duration of lamivudine therapy ($r=0.51$, $P=0.039$) (Fig. 1).

Resistance to Lamivudine

The mean overall estimate for lamivudine resistance was 18% (95% CI, 10%–37%). Lamivudine resistance was found in 8 (57%) of 14 studies, with large variation in reported rates (10%–42%). In three studies, sequence analysis was made and mutations in the YMDD locus of the HBV-DNA gene polymerase were observed. In other cases, no sequencing analysis was performed, but resistance was inferred by return of serum HBV-DNA during therapy. There was a positive association between frequency of lamivudine resistance and prolonged duration of lamivudine therapy ($r=0.62$, $P=0.019$).

Side Effects of Lamivudine

Only 2 (14%) of 14 studies reported any drug-related dropouts. Overall, 4 (2.1%) of 184 RT recipients discontinued the drug. Three patients stopped therapy because of minor side effects (nonspecific gastrointestinal tract complaints, paresthesia, erythema) after 1 week, 4 months, and 5 months of treatment, respectively. Two patients had muscle pain; in one of them, drug was withdrawn. In another patient, a dose reduction was required because of diarrhea.

TABLE 2. Baseline characteristics of the study patients

Authors	HBsAg-positive patients (%)	HBeAg-positive patients (%)	HBV-DNA–positive patients (%)	HBeAb-positive patients (%)	Raised ALT (%)
Rostaing et al., 1997[7]	6 (100)	1 (17)	6 (100)	5 (83)	5 (83)
Goffin et al., 1999[9]	4 (100)	1 (25)	4 (100)	3 (75)	4 (100)
Jung et al., 1998[8]	6 (100)	3 (50)	6 (100)	NA	6 (100)
Kletzmayr et al., 2000[15]	19 (100)	12 (63)	16 (84)	7 (37)	3 (16)
Tsai et al., 2000[14]	11 (100)	NA	8 (73)	NA	11 (100)
Lewandowska et al., 2000[11]	28 (100)	26 (93)	10 (36)	NA	28 (100)
Antoine et al., 2000[13]	12 (100)	12 (100)	12 (100)	NA	NA
Mouquet et al., 2000[12]	15 (100)	4 (27)	15 (100)	NA	15 (100)
Fontaine et al., 2000[10]	26 (100)	13 (50)	26 (100)	13 (50)	NA
Lee et al., 2001[18]	13 (100)	8 (61)	13 (100)	5 (38)	13 (100)
Han et al., 2001[16]	6 (100)	3 (50)	6 (100)	NA	6 (100)
Chan et al., 2002[20]	26 (100)	14 (54)	26 (100)	NA	14 (54)
Park et al., 2002[19]	10 (100)	5 (50)	10 (100)	NA	10 (100)
Mosconi et al., 2001[17]	4 (100)	NA	4 (100)	NA	4 (100)

NA, Not available; HBeAb, positive for antibody to HBeAg.

TABLE 3. Details of lamivudine therapy in clinical trials

Authors	No. of patients	Lamivudine dose (mg/day)	Lamivudine duration (mo)
Rostaing et al., 1997[7]	6	100	6
Goffin et al., 1999[9]	4	100	12
Jung et al., 1998[8]	6	100	8
Kletzmayr et al., 2000[15]	19	100	12
Tsai et al., 2000[14]	11	100	NA
Lewandowska et al., 2000[11]	28	75–150	4
Antoine et al., 2000[13]	12	NA	9
Mouquet et al., 2000[12]	15	50–100	6
Fontaine et al., 2000[10]	26	100	16
Lee et al., 2001[18]	13	100–150	12
Han et al., 2001[16]	6	100	12
Chan et al., 2002[20]	26	100	32
Park et al., 2002[19]	10	100–150	35
Mosconi et al., 2001[17]	4	50–100	23

NA, Not available.

TABLE 4. Outcomes of clinical trials

Authors	ALT normalization (%)	HBsAg clearance (%)	HBeAg clearance (%)	HBeAg seroconversion (%)	HBV-DNA clearance (%)
Rostaing et al., 1997[7]	4/5 (80)	0	0	NA	6/6 (100)
Goffin et al., 1999[9]	4/4 (100)	0	0	0/1 (0)	4/4 (100)
Jung et al., 1998[8]	6/6 (100)	0	1/3 (33)	NA	6/6 (100)
Kletzmayr et al., 2000[15]	3/3 (100)	0	2/12 (17)	2/12 (17)	15/16 (93)
Tsai et al., 2000[14]	NA	0	0	NA	7/8 (87.5)
Lewandowska et al., 2000[11]	17/28 (61)	0	2/26 (8)	NA	10/10 (100)
Antoine et al., 2000[13]	NA	0	8/12 (67)	NA	9/12 (75)
Mouquet et al., 2000[12]	8/15 (53)	0	NA	NA	13/15 (87)
Fontaine et al., 2000[10]	NA	0	6/13 (46)	6/13 (46)	26/26 (100)
Lee et al., 2001[18]	NA	1/13 (8)	3/8 (37.5)	3/8 (37.5)	10/13 (77)
Han et al., 2001[16]	6/6 (100)	0	2/3 (67)	NA	6/6 (100)
Chan et al., 2002[20]	14/14 (100)	0	3/14 (21)	NA	26/26 (100)
Park et al., 2002[19]	8/10 (80)	0	1/5 (20)	NA	7/10 (70)
Mosconi et al., 2001[17]	NA	0	NA	NA	4/4 (100)

NA, Not available.

TABLE 5. Histologic features and side effects caused by lamivudine

	Cirrhosis (%)	Pre- and posttreatment liver biopsy	Dropout rate (%)	Lamivudine resistance (%)
Rostaing et al., 1997[7]	2/6 (33)	0	0/6 (0)	0
Goffin et al., 1999[9]	1/3 (33)	0	0/4 (0)	1/4 (25)
Jung et al., 1998[8]	NA	0	0/6 (0)	0
Kletzmayr et al., 2000[15]	NA	0	3/19 (16)	3/12 (25)
Tsai et al., 2000[14]	NA	0	0/11 (0)	0
Lewandowska et al., 2000[11]	4/28 (14)	0	1/28 (4)	0
Antoine et al., 2000[13]	NA	2/12 (17)	0/12 (0)	0
Mouquet et al., 2000[12]	6/15 (40)	0	0/15 (0)	4/15 (27)
Fontaine et al., 2000[10]	8/26 (31)	0	0/26 (0)	8/26 (31)
Lee et al., 2001[18]	NA	0	0/13 (0)	1/4 (25)
Han et al., 2001[16]	1/6 (17)	0	0/6 (0)	3/6 (50)
Chan et al., 2002[20]	0/26 (0)	0	0/26 (0)	11/26 (42)
Park et al., 2002[19]	0/10 (0)	0	0/10 (0)	1/10 (10)
Mosconi et al., 2001[17]	NA	2/4 (50)	0/4 (0)	0

NA, Not available.

Completion of Lamivudine Therapy

Discontinuation of lamivudine use was reported in four (28%) studies. Overall, 51 (28%) of 184 RT recipients were observed after completion of lamivudine therapy. Twenty-nine (57%) of 51 patients had relapse of HBV-related liver disease with reappearance of HBV-DNA in serum and elevated ALT activity.

DISCUSSION

Interferon (IFN) therapy has been initially considered in the treatment of HBV-related liver disease after RT. Limited data on monotherapy with IFN in RT recipients with chronic HBV are available; few HBsAg-positive patients have been successfully treated with IFN (*1*, *29*). IFN use after RT is complicated by precipitation of graft rejection, which is

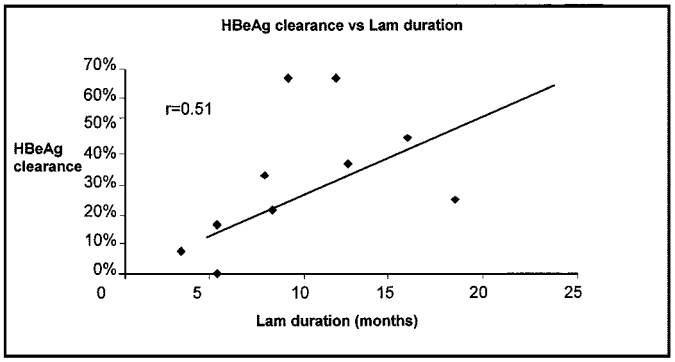

FIGURE 1. Relationship between the duration of lamivudine therapy and the percentage of patients achieving HBeAg clearance for each of the included studies reporting this outcome endpoint. Lam, Lamivudine.

mostly irreversible and steroid resistant (*1*, *3*). The approval of lamivudine, an oral nucleoside analog, has led many centers to use it after RT (*30*). Our meta-analysis confirmed the efficacy of lamivudine in the treatment of HBV-related liver disease after RT. The mean overall estimate for HBV-DNA and HBeAg clearance was 91% (95% CI, 86%–96%) and 27% (95% CI, 16%–39%), respectively. The mean overall estimate for ALT normalization was 81% (95% CI, 70%–92%). These response rates showed that lamivudine was effective in the immunosuppressed population; its efficacy in patients with normal immune activity or in those with immune compromise caused by uremia had already been shown. Thus, Lai et al. (*4*) reported that HBV-DNA suppression and ALT normalization were 98% and 72%, respectively, after 1 year of lamivudine therapy in patients with chronic hepatitis B and preserved renal function; the HBeAg seroconversion was 17%. A pilot study (*26*) in potential candidates for kidney or combined kidney-liver transplantation reported 100% suppression of HBV-DNA and ALT normalization with lamivudine treatment (10–40 mg daily for 12–26 weeks). The efficacy of lamivudine has also been demonstrated in reports describing the successful management of fibrosing cholestatic hepatitis by lamivudine in RT recipients (*30*). This is a severe form of HBV-related liver disease having typically a universally fatal outcome within a few months of onset.

Tolerance to lamivudine was very good; only 4 (2.1%) of 184 patients discontinued the drug because of side effects, which were minor. Tolerance to nucleoside analogs had been a concern in immunocompetent patients with HBV, given the prior experience with a lethal form of mitochondrial toxicity with fialuridine, an investigational nucleoside analog for chronic hepatitis B. However, nonimmunosuppressed patients who received lamivudine had a low incidence of adverse effects similar to placebo recipients (*4*).

The current meta-analysis has some shortcomings. Paired liver biopsy specimens were not available for most patients before and after therapy: reduction of necroinflammatory activity and fibrosis are important endpoints of antiviral therapy. Overall, only four patients had histologic analysis at the beginning and the end of lamivudine use—a significant improvement in inflammatory score was noted. Nephrologists are typically reluctant to request liver biopsies in patients with end-stage renal disease because of abnormalities in coagulation related to uremia. Another potential weakness was the scarcity of information at the completion of lamivudine treatment. Only 51 (28%) RT recipients were followed after lamivudine therapy; 57% of them experienced reactivation of HBV-related liver disease after completion of lamivudine. A recent multicenter survey in immunocompetent patients from the United States had reported that the virologic response was maintained 16 weeks after the end of treatment in 81% of those patients with loss of HBeAg from serum (*5*). Patients treated for 12 months had a slower return of detectable HBV-DNA in serum compared with patients treated for 3 or 6 months (*3*). Thus, it appears that the rate of reactivation after lamivudine withdrawal may be higher than in the immunocompetent population. Additional limitations were that the duration of therapy with lamivudine was variable; also, most trials lacked standardized clinical or laboratory criteria for lamivudine treatment; this might be related to the high number of possible endpoints. Nevertheless, treatment was directed to reactivation of HBV after RT in the majority of trials, and de novo acquisition of HBV after RT was infrequent in this population. Another potential issue is the type of HBV-DNA test in use, as all of these studies were performed with molecular hybridization technique, which is less sensitive than polymerase chain reaction-based technology. However, the endpoints of HBeAg loss and HBeAg seroconversion are not dependent on laboratory methods. As with all meta-analyses, this study has the potential limitation of publication bias. It is likely that negative trials were not published; obtaining data from as many sources as possible is a reliable approach to this issue. In contrast, we have not included trials in preliminary format (abstracts). This meta-analysis was based on an intent-to-treat principle, and preliminary data usually require efficacy analysis, as the dropout rate may be not reported. Clearly, calculating a response rate without accounting for the number of dropouts may overestimate the treatment efficacy (*31*).

The current meta-analysis revealed a high rate of lamivudine resistance. Lamivudine resistance was significantly and positively associated with prolonged drug use. Sequence analysis was performed in some cases, confirming the emergence of HBV mutants. It has been suggested that the rate of mutant emergence is greater in the immunocompromised population, including transplant recipients (*30*). Numerous newer agents with activity against YMDD mutants and wild-type HBV are in clinical trials. Famciclovir has been successfully used in the treatment of YMDD HBV mutants after RT (*30*); adefovir can be an effective treatment for lamivudine-resistant HBV mutants and wild-type HBV (*32*).

Several issues remain unanswered with regard to the treatment of HBV-related liver disease after RT. These include the optimal time to initiate lamivudine, the optimal duration of lamivudine use, and the role for pretransplantation therapy. Chan et al. suggested that incorporation of lamivudine therapy improved post-RT outcome if initiated within several months rather than several years of RT (*20*). Because of the scarcity of histologic data, the number of treated patients with cirrhosis or bridging cirrhosis was too small to elucidate differences in posttransplantation outcome when compared with patients having less advanced liver disease. Despite these limitations, the current meta-analysis showed that the therapeutic benefit of lamivudine after RT

has been encouraging in terms of suppression of HBV viremia and aminotransferase normalization.

CONCLUSION

Our meta-analysis showed that the majority of RT recipients with HBV-related liver disease had high virologic and biochemical response to lamivudine use. The drug was well tolerated. Lamivudine resistance was frequent, however, in RT recipients who received a prolonged course of therapy. Several points remain to be defined regarding the management of HBV-related liver disease after RT.

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