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EFFICACY OF LAMIVUDINE THERAPY FOR ADVANCED LIVER DISEASE IN PATIENTS WITH PRECORE MUTANT HEPATITIS B VIRUS INFECTION AWAITING LIVER TRANSPLANTATION¹

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Background. Orthotopic liver transplantation (OLT) for end-stage liver disease resulting from hepatitis B virus (HBV) infection is associated with a high rate of recurrence and reduced survival. Lamivudine is effective in inhibiting HBV replication in patients with chronic hepatitis. This study evaluated the impact of lamivudine on viral suppression, liver function, and disease severity in patients awaiting OLT with HBV e-minus strain infection.

Methods. Twenty-five patients received lamivudine (100 mg per day) from the day of listing for OLT. All patients were positive for serum HBV-DNA by polymerase chain reaction and all had a Child-Pugh score of 7 or higher.

Results. Patients were followed for 12±9 months (mean ± SD). Eleven underwent OLT within 13 months of treatment initiation, one died after 10 months, and one dropped out after 3 months. After 3, 6, and 9 months, HBV-DNA by polymerase chain reaction was undetectable in 14 of 25, 14 of 20, and 13 of 15 patients, respectively. Two patients developed lamivudine resistance after 9 and 18 months of treatment, respectively, without liver decompensation. Comparing baseline to last visit data, a significant improvement in prothrombin activity (43±15% vs. 52±19%; $P=0.0014$), serum bilirubin (3.4±1.9 vs. 2.5±2.2 mg/dL; $P=0.0007$), serum albumin (3.3±0.3 vs. 3.6±0.5 g/dL; $P=0.0278$), presence of ascites (15/25 vs. 7/25; $P=0.0047$), and Child-Pugh score (9 vs. 8; $P=0.0003$) was observed. Because of liver function improvement, four patients were placed on low priority status for OLT (United Network of Organ Sharing 3) and 9 on

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inactive status (United Network of Organ Sharing 7). The overall probability of survival at 6 and 12 months was 100% and 90.9%, respectively.

Conclusions. Lamivudine has an important role in patients with end-stage liver disease caused by HBV precore mutant strain. Not only does HBV-DNA suppression allow patients to be eligible for OLT, but the improvement of the patients' clinical status may delay the need for OLT in an era of organ shortage.

Chronic hepatitis B is one of the most widespread viral infections worldwide, potentially leading to liver cirrhosis and hepatocellular carcinoma (HCC) (1). Patients with decompensated disease and small HCC are candidates for orthotopic liver transplantation (OLT). However, when pretransplantation viral replication is present, a recurrence of hepatitis B virus (HBV) infection in the graft is usual (2) and often aggressive, with rapid progression to cirrhosis (3). These findings have led many centers to exclude patients with active HBV infection from candidacy for liver transplantation. During the last decade, treatment with interferon- α has been attempted with contrasting results (4,5). Furthermore, despite the use of low doses of interferon, such treatment is often associated with severe complications, for instance bacterial infections and severe liver cell necrosis, that can lead to worsening of the disease and even death.

Recently, lamivudine, a nucleoside analog able to suppress HBV replication through the inhibition of HBV-DNA synthesis by interfering with the reverse transcriptase activity, has become available. Several studies have demonstrated that lamivudine given to patients with HBV-compensated disease induces the suppression of viral replication and alanine aminotransferase (ALT) normalization within 1 to 2 months of treatment in the majority of cases (6,7). The drug has also been used in patients with decompensated cirrhosis, and highly promising results have been reported as suppression of viral replication and disease improvement were obtained (8-15).

The aim of this study was to evaluate the effects of viral suppression by lamivudine on liver function and disease severity in a cohort of HBV-positive cirrhotic patients infected with HBV e-minus strain who were candidates for liver transplantation.

MATERIALS AND METHODS

From April 1997 to November 1999, 52 white patients with decompensated cirrhosis caused by hepatitis B were evaluated for liver transplantation at our center. Thirty-seven were listed for OLT and, among them, 25 were enrolled in this prospective open study based on the following: (1) presence of hepatitis B surface antigen in serum for at least 6 months before evaluation; (2) positivity of serum HBV-DNA by solution hybridization assay, polymerase chain reaction assay (PCR), or both; (3) absence of hepatitis B e antigen in serum; (4) absence of ALT flares in the last 6 months; (5) Child-Pugh score of 7 or higher; (6) absence of HCC; and (7) absence of coinfection with hepatitis C virus, hepatitis D virus, and human immunodeficiency virus, retransplantation, other antiviral therapies, drug abuse, transjugular intrahepatic portosystemic shunt, and pregnancy.

Patients started lamivudine 100 mg at the time they were listed for OLT, after providing written informed consent. The study was approved by the local ethics committee. The patients were followed at our outpatient clinic every month, and clinical and biochemical parameters were evaluated. The patients received therapy for complications of liver disease (such as diuretics, antibiotic prophylaxis

against spontaneous bacterial peritonitis, and lactulose) and were supplemented with albumin infusion based on the following schedule: if serum albumin was less than 2.5 g/dL: 60 g weekly; from 2.5 to 3 g/dL: 40 g weekly; from 3.1 to 3.5 g/dL: 20 g weekly. The follow-up started at the beginning of lamivudine therapy and ended at the time of liver transplantation or death. At baseline and every 3 months, the following data were recorded in a data base: Child-Pugh score and its determinants; complete serology for HBV; serum HBV-DNA by solution hybridization assay (Abbott Laboratories, North Chicago IL; HBV-DNA lower detection limit = 1 pg/mL), or, if negative, HBV-DNA by qualitative PCR (in-house PCR assay with a detection limit of 250-500 genome copies per milliliter). Serum albumin, prothrombin activity, bilirubin, and ALT were measured with standard procedures. HBV genotypic analysis was performed using the restriction length fragment polymorphism assay as described in Lai et al. (7), whenever patients had evidence of viral breakthrough, defined as reappearance of serum HBV-DNA by PCR on two occasions at least 1 month apart after prior demonstration of negative results.

Statistical Analysis

Results are expressed as mean \pm SD or median and range when appropriate. The Friedman test was used to compare the change of repeated measures of Child-Pugh score and biochemical variables (serum albumin, prothrombin activity, bilirubin, and ALT) during the follow-up; for the dichotomous variables (ascites, encephalopathy, and positivity of HBV-DNA), the Cochran Q test was performed. Survival curves were evaluated using the Kaplan-Meier method with log-rank test; the patients who subsequently underwent OLT were considered as having dropped out of the study. Comparisons between groups were made using the chi-square test with Yates correction or the Mann-Whitney U test for independent samples, as appropriate. A P value of less than 0.05 was considered statistically significant. All analyses were conducted with SPSS 6.0 software (SPSS Inc., Chicago, IL).

RESULTS

The baseline characteristics of patients are reported in Table 1. Patients were followed for 12 \pm 9 months.

TABLE 1. Characteristics of patients at enrollment

Characteristic	Baseline data ^a
Gender (M/F)	22/3
Age (yr)	50 \pm 8
Encephalopathy present, n (%)	5 (20%)
Ascites present, n (%)	15 (60%)
Albumin (g/dL)	3.3 \pm 0.3
Bilirubin (mg/dL)	3.4 \pm 1.9
Prothrombin activity (%)	43 \pm 15
Child-Pugh class, n (%)	
B	13 (52%)
C	12 (48%)
Child-Pugh score	9 (7-13) ^b
Number of patients treated with albumin intravenously, n (%)	20 (80%)
ALT (U/L)	105 \pm 80
HBV-DNA positive by solution hybridization, n (%)	19 (76%)
HBV-DNA by solution hybridization (pg/mL)	36 \pm 49
HBV-DNA positive by PCR, n (%)	25 (100%)

^a Results are expressed as mean \pm SD.

^b Expressed as median and range.

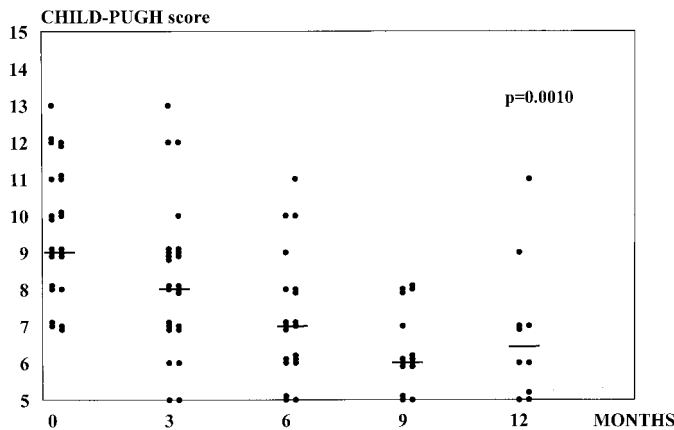


FIGURE 1. Changes in Child-Pugh score of patients treated with lamivudine. The lines indicate the median. When overlapping occurred at a particular numeral score, the points were slightly separated to allow better discrimination of the distinct responses.

Virologic Response and Safety

At the start of lamivudine therapy, all patients had serum HBV-DNA detectable by solution hybridization assay (19 patients, 76%) or by PCR. All of them remained positive for hepatitis B surface antigen during the observation period.

All treated patients were followed up for at least 3 months. At that time, 23 patients (92%) were negative for serum HBV-DNA at the solution hybridization assay and, among them, 14 (56%) were also negative at the PCR. After 6 months, when 20 patients were still in follow-up, all but one were negative for HBV-DNA at the solution hybridization assay; 14 (70%) also tested negative at the qualitative assay. The only patient still positive at the quantitative assay after the sixth month of therapy became negative at the seventh month. Among the six patients who still tested positive at the qualitative assay, two tested negative for HBV-DNA after 9

TABLE 2. Comparison of Child-Pugh parameters and score during the observation period

Child-Pugh parameters	Baseline ^a	Last visit ^a (12±9 months)	P
Encephalopathy, n (%)	5 (20%)	2 (8%)	NS
Ascites, n (%)	15 (60%)	7 (28%)	0.0047
Bilirubin (mg/dL)	3.4±1.9	2.5±2.2	0.0007
Albumin (g/dL)	3.3±0.3	3.6±0.5	0.0278
Number of patients treated with albumin intravenously, n (%)	20 (80%)	9 (36%)	0.0009
Prothrombin activity (%)	43±15	52±19	0.0014
Child-Pugh score	9 (7–13) ^b	8 (5–12) ^b	0.0003

^a Results are expressed as mean±SD.

^b Expressed as median, with range in parentheses.

months of treatment, two underwent OLT at the 7th and 8th month when still positive, and two were still positive at the 9th and 12th month of treatment.

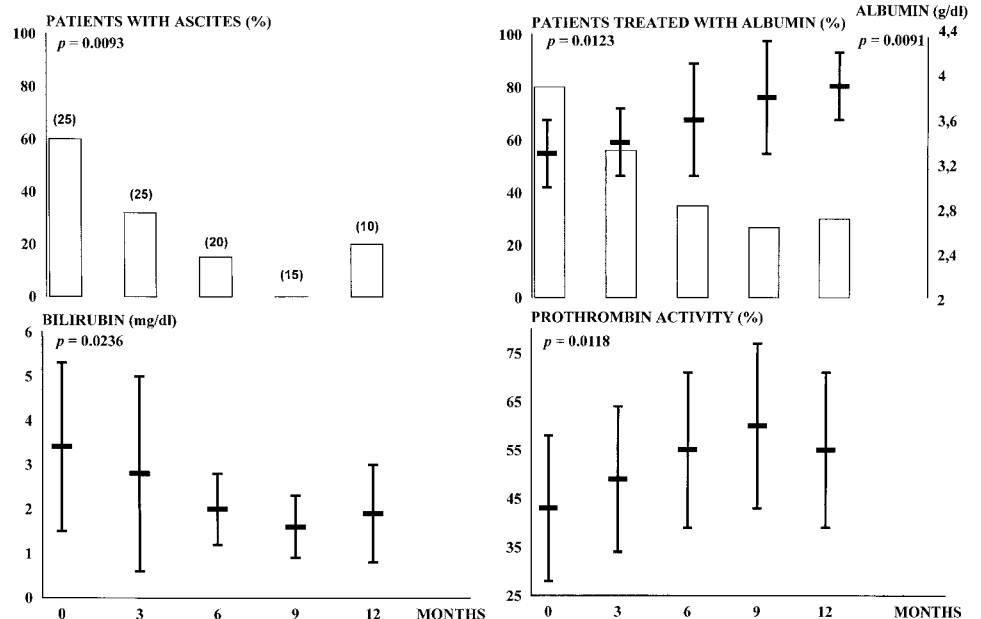
Only two patients developed lamivudine resistance after 9 and 18 months of treatment, respectively, which was not associated with ALT flare. The cumulative rate of resistance was 6.7% after 1 year of treatment and 25.3% after 18 months. The resistance was confirmed to be a result of the characteristic mutations in the YMDD motif of the HBV-DNA polymerase. Lamivudine treatment was continued, and no deterioration of patient conditions occurred up to 9 months from the development of resistance. No untoward effects of lamivudine were observed.

Liver Function and Clinical Status

Mean ALT levels after 3 (48±29 U/L) and 6 months (41±22 U/L) significantly decreased compared with baseline (105±80 U/L; P<0.0001).

At enrollment, 13 patients belonged to Child-Pugh class B and 12 to class C, with a median score of 9. At the last visit, which was performed after 3 to 35 months, a significant reduction of the median score was observed (8 vs. 9;

FIGURE 2. Mean (±SD) albumin, bilirubin, and prothrombin activity values. Boxes represent percentage of patients with ascites and treated with albumin intravenously; figures in parentheses report the number of patients followed up.



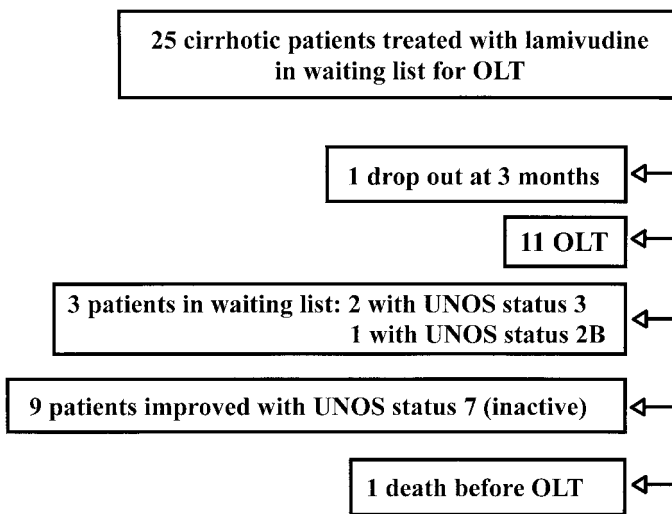


FIGURE 3. Clinical outcome.

$P=0.0003$). An improvement of at least 2 points was detected in 12 patients (48%); the median time interval between commencement of lamivudine and improvement in Child-Pugh score of 2 or more points was 3 months, with a range from 3 to 9 months. Thus, at the last visit, 6 of the 13 Child-Pugh B patients improved to Child-Pugh A and 6 remained as Child-Pugh B, with only one worsening to Child-Pugh class C. Of the 12 patients who were Child-Pugh C at entry, 5 improved to Child-Pugh A, 4 to Child-Pugh B, and 3 remained as Child-Pugh C. Interestingly, in 10 patients who did not undergo transplantation within the first year, 5 (50%) had a clinical improvement resulting in a reduction in Child-Pugh score of 2 or more points.

Among the six patients with HBV-DNA detectable only by PCR at baseline, two cases showed an improvement of liver function (from Child-Pugh C to A and from Child-Pugh C to B, respectively), three remained in the same Child-Pugh class, and only one worsened from Child-Pugh class B to C because of portal vein thrombosis development causing disease decompensation after 12 months of therapy.

Considering all patients, the improvement in Child-Pugh score was progressive throughout the observation period (Fig. 1) and was a result of changes in all its components, such as plasma bilirubin and albumin concentrations, prothrombin activity, and presence of ascites (Fig. 2 and Table 2). The requirements of albumin infusion (Fig. 2) and diuretic therapy decreased from baseline to the last visit (spironolactone: 194 ± 85 mg per day vs. 144 ± 96 mg per day; $P=0.028$; furosemide: 10.5 ± 11 mg per day vs. 5.5 ± 8 mg per day; $P=0.1$). Similarly, the number of patients with ascites requiring paracentesis decreased from baseline to the last visit without reaching statistical significance (5/15 vs. 2/15; $P=0.083$).

Survival and Liver Transplantation

The outcome of patients is summarized in Figure 3. The overall probability of survival at 6 and 12 months was 100% and 90.9%, respectively. One patient died because of spontaneous bacterial peritonitis after 10 months of treatment, and one dropped out during the follow-up because of referral to another transplant center. Eleven patients underwent OLT:

three within 6 months of treatment and eight after 7 to 13 months. Two of these patients had changed their status on the United Network of Organ Sharing (UNOS) waiting list (16) to low priority (from status 2B to 3), whereas two remained at status 2B and five at status 3; the remainder were reclassified to status 2B from 3, because of HCC development and deterioration of liver function, respectively. After liver transplantation, nine patients are alive, in good condition and without viral reinfection after a median period of 30.5 months, while two died shortly after because of perioperative complications or hyperacute rejection. All transplant patients were treated with immunoglobulin prophylaxis in association with lamivudine therapy after OLT.

Three patients are still on the waiting list, two have been reclassified to low priority (from UNOS status 2B to 3), and one worsened to status 2B after 12 months. The remaining nine patients have been placed on the inactive status for OLT (four patients from 2B to 7 and five from 3 to 7).

DISCUSSION

It has been clearly shown that lamivudine effectively suppresses HBV replication in patients with chronic hepatitis (6,7,17). Up to now, eight studies published in extensive form have evaluated the effects of lamivudine treatment in the setting of advanced HBV-related cirrhosis (8–15). As a whole, the results obtained showed that the drug is able to suppress HBV replication also in this context and, more importantly, this is followed by stabilization of the disease process and even an improvement in the severity of the disease.

The present study fully confirmed these findings: HBV-DNA disappeared from serum within 2 months of treatment in all cases except two (who became HBV-DNA negative after 3 and 7 months, respectively), a time span also recorded in well-compensated HBV-related liver disease (18). Moreover, the disease severity, as assessed by calculating the Child-Pugh score, either remained steady or improved in all patients except one.

We also provided additional and, in some respects, more reliable information with respect to the available studies dealing with this matter. In fact, several studies enrolled a rather low number of patients (8,9,11–13); to date, besides those recently reported by Villeneuve et al. (10), Perrillo et al. (14), and Yao et al. (15), our patients represent the largest cohort investigated prospectively. Moreover, the group of patients we enrolled was fairly homogeneous, because we avoided including subjects with acute decompensation after ALT flares, a rather common event in chronic HBV hepatitis (19). Even though this can have severe or even fatal consequences, spontaneous recovery can also occur (19). Thus, it is possible that the effects of lamivudine treatment in patients with acute decompensation may not be completely ascribed to the antiviral therapy. Contrary to this, our patients stabilized or improved their conditions in a clinical setting in which a relentless worsening should be expected. The homogeneity of our patients also derived from the fact that only subjects infected by HBV precore mutant strain were included, whereas the previous studies enrolled patients infected by both wild-type and precore mutant HBV strains and patients coinfecting with other hepatotropic viruses, such as hepatitis C virus and HDV (10–12,14,15). Thus, the present study demonstrated that lamivudine also succeeds in suppressing HBV replication and stabilizing or improving

the disease severity in patients with advanced cirrhosis caused by HBV precore mutant strain. This finding is of particular interest in the Mediterranean area, where more than 95% of HBV patients are infected by this strain (20).

It is important to point out that the favorable effects of lamivudine treatment were not limited to the improvement of liver function tests but also involved the clinical status of our patients, as evaluated by the Child-Pugh score system, human albumin requirement, diuretic dosage, and the need for paracentesis. Interestingly, this improvement was rapid; in fact, a significant clinical response based on the change in Child-Pugh score was observed within 3 months from the start of therapy in most patients. Only in two cases was this response seen after 9 months of treatment. Moreover, only one patient developed major complications of cirrhosis, such as gastrointestinal bleeding, spontaneous bacterial peritonitis, and hepatorenal syndrome.

The availability of lamivudine is particularly relevant in the liver transplant setting. In fact, its effects on viral replication allow listing for OLT patients with active HBV replication and can help in reducing the incidence of HBV infection recurrence after OLT. In this respect, all our patients became HBV-DNA negative, as reported above, and none of the nine patients who survived OLT developed HBV infection recurrence after a median follow-up period of 30.5 months. Furthermore, the efficacy of lamivudine in stabilizing or improving the clinical conditions of patients awaiting OLT could reduce the financial impact of pretransplantation medical care and ameliorate their postoperative outcome. In fact, prognostic models have demonstrated that patient survival after OLT depends on pretransplantation clinical and laboratory status (21,22). We examined the potential therapeutic benefit of lamivudine on UNOS status. Thirteen (52%) patients improved their UNOS status and, among them, nine improved sufficiently to be removed from the active waiting list for OLT, having reached UNOS status 7. Three patients had to be reclassified to a higher priority, one because of HCC development and the remainder because of deterioration of clinical conditions. With regard to these last two patients, the deterioration of liver function was caused in one case by a treatment failure, with a progressive impairment of the clinical conditions despite lamivudine treatment. In the other, we observed a good therapeutic response to therapy, but after 10 months the patient suddenly developed a portal vein thrombosis with rapid deterioration of liver function.

The results obtained in the present study are therefore important because patients were able to either undergo OLT in better or, at least, preserved conditions with respect to the time of listing, or even delay the need for OLT, which can be relevant in an era of organ shortage.

A major concern about lamivudine treatment is the selection of viral-resistant mutants, which occur with an incidence of about 15% to 30% after the first year of treatment in patients with chronic hepatitis B (8,9). In our study, only two patients developed lamivudine resistance, as defined by the reappearance of HBV-DNA in serum. Such a low rate of resistance development could be related to the short follow-up duration, because it has been shown that the rate of detection of resistant HBV strains increases with the length of treatment (23). Thus, prolonging the stay on the waiting list because of improvement in the UNOS status may increase the risk of selecting lamivudine-resistant strains. Al-

though our patients who developed resistant strains continued to have low serum HBV-DNA and ALT levels and their clinical condition did not deteriorate, it cannot be forgotten that severe and even fatal flares have been reported to follow the selection of resistant strains (24,25). Moreover, patients with pretransplantation lamivudine-resistant viral strains may have an increased risk of recurrent hepatitis B after OLT. Finally, delaying OLT could also expose patients to a higher risk of developing HCC. Unfortunately, an antiviral agent that is safe and effective in suppressing lamivudine-resistant mutants, such as adefovir dipivoxil, is potentially nephrotoxic and its long-term safety in patients with decompensated cirrhosis has not yet been established (26). Thus, the risk of developing lamivudine-resistant viral strains and HCC remains an unresolved issue, which makes the choice of the starting time of treatment crucial. Based on the limited data available, we started lamivudine in patients with decompensated HBV cirrhosis at the time they were listed for OLT, in the hope of decreasing the length of treatment before transplantation, avoiding lamivudine administration during the time spent to complete the study protocol setting the listing criteria for OLT.

CONCLUSION

Our study demonstrated that lamivudine treatment is safe and effective in patients with end-stage liver disease caused by HBV precore mutant strain. In fact, viral replication was suppressed in all patients, and no infection recurrence occurred in those who underwent OLT. Moreover, most patients either improved or stabilized their UNOS status while awaiting transplantation, and some patients were removed from the active waiting list. However, the risk of developing lamivudine-resistant HBV strains and HCC during the prolonged stay on the waiting list remain unresolved issues that should be evaluated in a larger cohort of patients.

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LONG-TERM OUTCOME OF LIVER RETRANSPLANTATION IN CHILDREN

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Background. Retransplantation of the liver is the only means of prolonging survival in children whose initial graft has failed. Patient and graft survival rates after retransplantation in most series have been inferior to rates after first transplantation.

Patients and methods. Of 450 pediatric liver transplantations performed between January 1990 and March 2001, 50 were first retransplantations, 9 were second retransplantations, and 1 was a third retransplantation. The overall retransplantation rate was 13.3% (median age at retransplantation 4 years and median weight 15 kg). The median post-retransplantation follow-up was 73 (range, 6-139) months.

Results. Kaplan-Meier patient survival rates for the group (n=50) were 71.7%, 64.7%, and 64.7% at 1, 3, and 5 years, respectively. Graft survival rates were 65.6%,

56.7%, and 56.7% at 1, 3, and 5 years, respectively. This is significantly worse than rates for children undergoing first liver transplantation. There were 17 deaths, of which 9 occurred in the first month. Biliary complications occurred in 5 (10%) patients and vascular complications in 6 (12%). Improved patient and graft survival rates were observed in the later phase of the program, although the difference was not significant. Higher preoperative serum creatinine ($P=0.001$) and serum bilirubin ($P=0.02$) levels were associated with a higher postoperative mortality.

Conclusion. Results of retransplantation in children remain inferior to those after first transplantation. There is a trend toward improving results. Liver retransplantation makes an important contribution to overall survival in children.

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The results of retransplantation have consistently been worse than those of primary transplantation, although they have been improving (1-4). There has been a vigorous debate regarding the allocation of grafts for retransplantation because up to 29% of children in some series have eventually needed to undergo retransplantation (1,5). However, retrans-