ORIGINAL ARTICLE

Underlying Disease as a Predictor for Rejection After Liver Transplantation

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Background: As significantly more patients die of infection than of rejection after liver transplantation, we have to conclude that overimmunosuppression is common. Our analysis was performed to investigate underlying disease as an appropriate parameter for individually reduced immunosuppression.

Design: A consecutive series of patients receiving primary liver transplantation was analyzed with regard to acute rejection.

Setting: Department of transplantation surgery in a university hospital.

Patients and Methods: From 1988 to 1995, 252 patients received liver transplantation for posthepatitic cirrhosis, alcoholic cirrhosis, cholestatic disease, or hepatoma and were analyzed in a univariate and multivariate manner.

Main Outcome Measure: The influence of various underlying diseases on the incidence of acute rejection.

Results: The estimated risk for freedom from acute rejection and analysis of cumulative rates of acute rejection stratified by group showed significant differences between the groups, except for alcoholic and posthepatitic cirrhosis. Severity of acute rejection episodes, as assessed by the need for rescue therapy, was similar in both univariate analysis and cumulative rates for alcoholic and posthepatitic cirrhosis. As expected, patients with cholestatic disease exhibited a significantly increased requirement for rescue therapy. For patients with hepatoma, a low incidence of initial and a high rate of repeated rescue therapy were observed. The varying immunological behavior within this group may have influenced both expansion of the tumor and severity of acute rejection. Multivariate analysis of potential risk factors identified underlying disease as a variable of independent prognostic significance for acute rejection and the need to receive rescue therapy.

Conclusion: These results indicate the importance of taking the original disease into consideration where immunosuppressive therapy is concerned.

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THE RESULTS of liver transplantation have improved over the past decade and the current 1-year survival rate exceeds 70%.[1,2] Analysis of the data indicates that the rate of improvement in the survival curves has slowed down during the past 2 years. The introduction of new immunosuppressive agents has not been associated with improved patient or graft survival.[3,4] The regimen relies predominantly on the administration of cyclosporine or tacrolimus in association with steroids and azathioprine. The addition of polyclonal or monoclonal antibodies in the early postoperative period, the use of targeted cyclosporine blood levels, and the duration of steroid administration vary between transplantation centers. However, within a given center, all patients usually receive the same immunosuppressive regimen because they are all considered to be at the same risk of rejection.

In many publications various parameters such as HLA-DR mismatch,[5-7] cytomegalovirus infection,[8,9] and preservation-induced injury[10,11] have suggested and failed to confirm an influence on rejection. Two studies recently discussed the importance of the effect of underlying disease on rejection[12,13] and showed a concrete connection between the original disease and rejection. In neither of the studies was individually adapted immunosuppression therapy realized as a consequence. However, this parameter seems to be becoming of greater interest in the management of immunosuppressive therapy, although it has not been possible to give a

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PATIENTS AND METHODS

STUDY POPULATION

From January 1988 to January 1995, 354 liver transplantations were performed on 307 patients at the Department of Transplant Surgery of the University of Vienna, Vienna, Austria. This study period was selected because there were no changes in the preoperative, intraoperative, or postoperative management during this time. The indication for transplantation was posthepatitic cirrhosis in 59 recipients, alcoholic cirrhosis in 60 recipients, cholestatic diseases in 42 recipients, and hepatoma in 91 recipients. Comparison of the groups was performed retrospectively. Recipients undergoing transplantation for other types of cirrhosis (n=16), metabolic disease (n=11), primary acute hepatic failure (n=17), and pediatric transplantations (n=11) were excluded from the analysis because of inhomogeneous and small groups. Therefore, 252 patients were eligible for analysis.

All patients with hepatoma and most of those with cirrhosis had had at least 1 liver biopsy preoperatively, and histological examination of the specimen had confirmed liver disease. The selection of patients with alcoholic cirrhosis was performed as described elsewhere.[14] The diagnosis of end-stage liver disease was based in each case on the history, compatible clinical and laboratory findings, and the morphology of the resected diseased liver after transplantation. Patients were generally considered for transplantation if liver function suggested a poor prognosis, such as a Child score of B or C or, in the case of hepatoma, in the absence of extrahepatic manifestation if resection was not possible.

PATIENT FOLLOW-UP

During hospitalization, a complete laboratory investigation (hematologic testing, liver function parameters, coagulation, electrolytes, total protein, renal parameters, electrophoresis, and lipid profile) as well as cyclosporine high-pressure liquid chromatography or monoclonal fluorescence polarization immunoassay whole-blood trough levels were determined daily. The outpatient follow-up intervals were usually once a week during the first month after discharge, twice monthly during the second and third months, monthly during the next 3 months, and every 2 or 3 months thereafter, regardless of the length of the observation period after the transplantation. A visit might also have been necessary at any time because of a particular problem. Complete laboratory investigations, as described earlier, were performed at each visit.

IMMUNOSUPPRESIVE REGIMEN

During the observation period, all patients received the same immunosuppressive regimen. Beginning 6 hours posttransplantation at the latest, rabbit antihuman thymocyte immunoglobulin (Thymoglobuline, Pasteur-Merieux, Lyon, France), 2.5 mg/kg of body weight, was given intravenously as a daily infusion during a 6-hour period. This induction therapy was continued for 10 days. Beginning on the eighth postoperative day, cyclosporine, 8 mg/kg per day, was administered orally in 2 doses and the dosage adjusted to obtain a trough whole-blood high-pressure liquid chromatography target level between 100 and 150 ng/mL (fluorescence polarization immunoassay, 150-200 ng/mL). An intravenous bolus of 40 mg of dexamethasone was given intraoperatively and tapered to 4 mg by day 5. Twenty milligrams of prednisolone was administered orally for 3 months thereafter. The dosage was decreased monthly by 5 mg to a maintenance dose of 5 mg of prednisolone after the fifth month. Azathioprine, 2 mg/kg per day, was administered after a successfully treated rejection episode as long-term triple therapy or if the current immunosuppressive double regimen with cyclosporine and steroids had to be reduced because of adverse events.

ASSESSMENT OF REJECTION

The diagnosis of rejection was made on clinical, laboratory, and histological findings. Development of fever and increasing indisposition of the patient, a rise in bilirubin and transaminase levels, and a change in color and amount of bile produced per day were regarded as possible signs of rejection. Biopsies were performed when clinically indicated, and always before the start of treatment. Severity of acute graft rejection in percutaneous liver needle biopsy was graded in categories[15,16] of mild, moderate, and severe rejection. Antirejection treatment was usually begun in the presence of moderate or severe rejection as determined by histological examination. Rejection requiring treatment was classified as a clinically relevant rejection episode. The diagnosis of recurrent acute rejection was considered when normal liver function test results had been obtained between the 2 rejection episodes.

RESCUE THERAPY

Clinically relevant rejection episodes were treated with 3 pulses of 100 mg of dexamethasone. If steroids failed, a course of 10 to 14 days of equine antihuman thymocyte globulin (Lymphoglobuline, Pasteur-Merieux; 10 mg/kg per day) treatment was usually initiated. Monoclonal murine anti-CD3 antibody (OKT3, Ortho-mune monoclonal antibodies, Ortho Diagnostic Systems Inc, Raritan, NJ; 5 mg/d) or rabbit antihuman T-lymphocyte globulin (ATG, Fresenius AG, Bad Homburg, Germany; 5 mg/kg per day) was administered to only a few patients, especially in the case of a second steroid-resistant acute rejection episode.

STATISTICAL ANALYSIS

Freedom from acute rejection episodes and freedom from antirejection therapy, as well as patient and graft survival, were calculated by the Kaplan-Meier method.[17] The Mantel[18] and Breslow[19] tests were used to find differences between proportions and the significance of associations. Cumulative rates of acute rejection episodes and receiving rescue therapy per patient per month and continuous demographical data (age, cold ischemia time, duration of operation, and anhepatic phase) were compared with the unpaired, 1-tailed t test. Differences in proportional demographic data (sex, Child score, crossmatch, and units of blood used) were calculated by univariate χ^2 analysis. The independent importance of potential risk factors was tested using the proportional hazards regression model of Cox.[20] A probability value of $P<.05$ was considered to be significant. At that time none of the 252 patients in the study group had been unavailable for follow-up.

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Table 1. Demographic Patient Characteristics

Variable	Alcoholic Cirrhosis	Posthepatitic Cirrhosis	Hepatoma	Cholestatic Disease	*P*
No. of patients	60	59	91	42	
Age, y					.07
Median	49	48	53	54	
Average (mean±SD)	48.6±8.4	46.5±14.4	51.0±11.2	51.7±9.9	
Sex, % male	82	66	69	21	.001
Child score, %					.001
B	20	26	40	27	
C	80	74	13	73	
Crossmatch, % negative	90	91	94	88	.19
Cold ischemia time, h					
Median	10.5	9.0	9.4	10.0	.45
Average (mean±SD)	12.3±3.9	9.5±3.7	9.6±2.9	10.0±3.8	
Duration of surgery, h					.42
Median	5.5	6.0	6.0	5.0	
Average (mean±SD)	5.9±1.7	6.0±1.8	5.8±1.3	5.4±1.2	
Anhepatic phase, min					.06
Median	93	90	90	84	
Average (mean±SD)	96.7±26.5	104.6±43.9	95.4±31.9	86.0±28.1	
Units of blood used					.20
Median	9.0	11.0	9.5	9.0	
Average (mean±SD)	13.4±11.1	12.7±8.8	12.5±10.8	9.5±5.9	

definite explanation for the varying initial immunological status of the patients.

Our study was performed to enlarge this spectrum of observations through comparison of the incidence of acute rejection in patients who had undergone transplantation for various original diseases. Analyzing the causes of death of all recipients who died at our center shows that 33% died of infectious complications and only 2% of rejection. Because the risk of infectious complications from immunosuppression was not balanced against the goal of preventing graft rejection, parameters need to be found for individually adapted immunosuppression therapy. In our clinical experience, underlying disease has been found to be an appropriate parameter for this purpose.

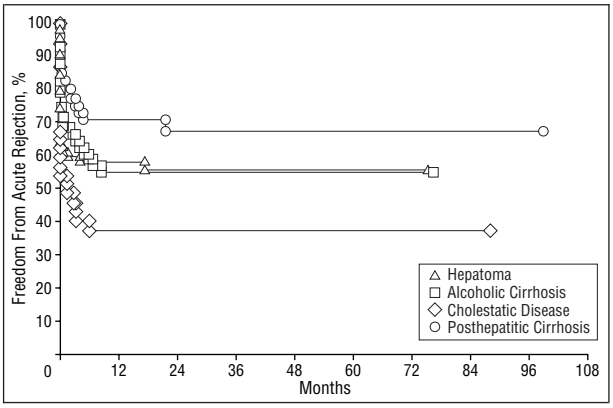

Figure 1. *Probability of freedom from acute rejection as a function of the underlying disease (hepatoma, n=91; alcoholic cirrhosis, n=60; cholestatic disease, n=42; and posthepatitic cirrhosis, n=59).*

RESULTS

PRETRANSPLANTATION CHARACTERISTICS

Demographic and transplantation characteristics of the 252 patients entered for analysis are summarized in **Table 1**. Sex as well as severity of liver disease at the time of transplantation were somewhat different between groups, reflecting differences in the epidemiology and timing of transplantation for each underlying disease. Parameters thought to influence the immune system (cytotoxic crossmatch, duration of operation, anhepatic phase, cold ischemic time, and units of blood used) were not statistically different and the groups were well matched.

ACUTE REJECTION

The overall 1-year incidence of acute rejection was 43%. This incidence was significantly different in patients who had undergone transplantation for cholestatic disease, those with hepatoma or alcoholic cirrhosis, and those undergoing transplantation for posthepatitic cirrhosis (Mantel $P=.02$, Breslow $P=.01$). The difference was mainly related to a reduced incidence of early (within the first 2-3 weeks posttransplantation) rejection episodes, whereas the incidence of late rejection episodes was comparable (**Figure 1**).

When compared by multivariate analysis, the underlying disease was the only variable of independent prognostic significance ($P=.002$). As expected, age, sex, units of blood used, and cold ischemic time did not influence acute rejection episodes (**Table 2**).

Cumulative rates of acute rejection episodes per patient per month were examined for months 1 to 6 for all groups of underlying disease (**Figure 2**). At 6 months, when 94% of all acute rejection episodes occurred, the cumulative rates of acute rejection were 0.45 for alcoholic cirrhosis, 0.55 for posthepatitic cirrhosis, 0.65 for hepatoma, and 1.00 for cholestatic disease. Only alco-

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Table 2. Acute Rejection, Cox Regression Analysis

Factor	*P*	Relative Risk	Coefficient
Sex*	.93	0.9	−0.072
Age	.63	1.0	0.003
Underlying disease†	.002	1.4	0.314
Units of blood used	.15	1.0	−0.020
Cold ischemia time	.46	1.0	0.007

**Male, 1; female, 2.*
†Posthepatitic cirrhosis, 1; alcoholic cirrhosis, 2; hepatoma, 3; cholestatic disease, 4.

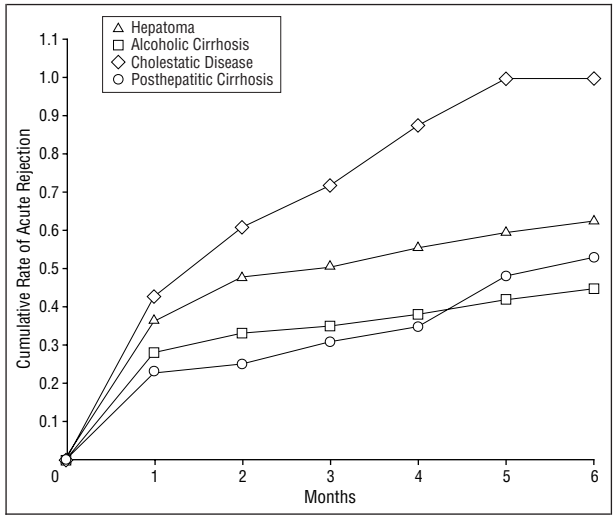

Figure 2. *Cumulative rates of acute rejection episodes per patient per month; patients undergoing transplantation for alcoholic cirrhosis vs posthepatitic cirrhosis vs hepatoma vs cholestatic disease.*

holic cirrhosis and posthepatitic cirrhosis showed no difference (*P*=.17). The comparison between all other groups reached statistical significance (alcoholic cirrhosis with cholestatic disease and hepatoma, *P*<.001 and *P*=.007, respectively; virus-related cirrhosis with cholestatic disease and hepatoma, *P*<.001 and *P*=.04, respectively; and cholestatic disease with hepatoma, *P*<.001).

RESCUE THERAPY

The incidence of receiving rescue therapy (**Figure 3**) was comparable in patients who had undergone transplantation for alcoholic or posthepatitic cirrhosis (15%). More patients who had undergone transplantation for hepatoma (23%) received rescue therapy and the highest figures were found in those who had undergone transplantation for cholestatic disease (33%). However, this trend did not reach statistical significance (Mantel *P*=.07, Breslow *P*=.06).

The Cox model identified the underlying disease (*P*=.03) and the units of blood used (*P*=.02) as independent predictors of receiving rescue therapy (**Table 3**). The influence of the latter variable on this issue cannot be explained.

The severity of acute rejection episodes was increased in patients with cholestatic disease, with more patients having 1 or more moderate or severe acute rejection episodes requiring treatment (**Figure 4**). The cumulative rates per patient per month at 6 months were 0.18 for alcoholic cirrhosis, 0.26 for posthepatitic cirrhosis, 0.32 for hepatoma, and 0.50 for cholestatic disease. The rates for alcoholic and posthepatitic cirrhosis (*P*=.17) and posthepatitic cirrhosis and hepatoma (*P*=.25) were not significantly different. A significant difference could be demonstrated between all the other groups (alcoholic cirrhosis with cholestatic disease and hepatoma, *P*<.001 and *P*=.04, respectively; cholestatic disease with posthepatitic cirrhosis and hepatoma, *P*=.02 and *P*=.03, respectively).

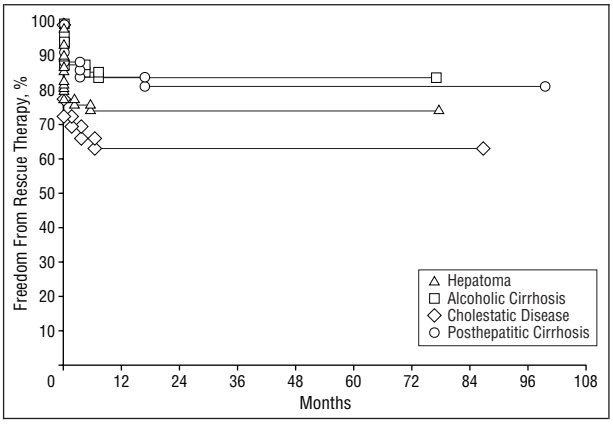

Figure 3. *Probability of freedom from rescue therapy as a function of the underlying disease (hepatoma, n=91; alcoholic cirrhosis, n=60; cholestatic disease, n=42; posthepatitic cirrhosis, n=59).*

Table 3. Rescue Therapy, Cox Regression Analysis

Factor	*P*	Relative Risk	Coefficient
Sex*	.14	0.8	−0.251
Age	.36	1.0	0.003
Underlying disease†	.03	1.2	0.194
Units of blood used	.02	1.0	0.025
Cold ischemia time	.40	1.0	0.008

**Male, 1; female, 2.*
†Alcoholic cirrhosis, 1; posthepatitic cirrhosis, 2; hepatoma, 3; cholestatic disease, 4.

STEROID-RESISTANT REJECTION

Steroid-resistant acute rejection was diagnosed in 5 patients (12%) with cholestatic disease, 6 patients (10%) with alcoholic cirrhosis, and 6 patients (6.6%) with hepatoma. It was significantly lower (1.7%; *P*=.02) only in posthepatitic cirrhosis. Despite a comparable incidence of steroid-resistant acute rejection, patients who had undergone transplantation for cholestatic disease received the highest cumulative dose of steroids per patient in comparison with the other groups (alcoholic cirrhosis, *P*<.001; virus-related cirrhosis, *P*=.001; and hepatoma, *P*=.004).

COMMENT

Important immunological factors in liver transplantation include graft rejection and the consequences of the

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immunosuppression therapy required to control it. Various parameters influencing acute rejection after orthotopic liver transplantation are currently under discussion. According to the results in kidney transplantation, the effect of HLA-DR mismatch was analyzed in retrospective studies[5-7] but the results were divergent. Similar observations were made for cytomegalovirus infection[8,9] and preservation-induced injury.[10,11] However, 2 recent studies[12,13] discussed the influence of the original disease on acute rejection. Both studies started out from the hypothesis that varying immunological initial situations of the transplantation candidates result from the original disease. The article from our institution[12] compared 2 very different immunological groups, primary biliary cirrhosis, meaning patients who suffer from an autoimmune disease accompanied by a hyperactive immune system, and alcoholic patients, representing patients with a preoperatively chronically weakened immune system. Farges et al[13] analyzed the incidence of acute rejection in patients undergoing transplantation for primary biliary cirrhosis, primary sclerosing cholangitis, alcoholic cirrhosis, autoimmune cirrhosis, and hepatitis B– and hepatitis C virus–induced cirrhosis. The authors found a low incidence of acute rejection for patients with alcoholic- and virus-induced cirrhosis. In contrast, patients who had undergone transplantation for an autoimmune disease (primary biliary cirrhosis, primary sclerosing cholangitis, or autoimmune cirrhosis) were at an increased risk of an acute rejection episode. The results in both publications were therefore comparable.

Farges et al[13] excluded patients with malignant disease in the native liver because they are at risk of recurrence and because they usually undergo chemotherapy posttransplantation. The purpose of our study was to compare the major groups of original diseases representing the indications for orthotopic liver transplantation at our transplantation center, including hepatoma. During the study period, none of these recipients received chemotherapy and 1-year patient survival was comparable to that of the other groups. Recurrence of disease did not usually occur in the 12 months after transplantation, whereas 94% of all acute rejection episodes occurred within the first 6 months.

Univariate analysis considered only the first episode of acute rejection, and with the occurrence of this event the patient was censored, thus indicating freedom from acute rejection. The incidence of freedom from acute rejection could be demonstrated to be significantly higher in patients undergoing transplantation for posthepatitic cirrhosis. In addition, steroid-resistant acute rejection episodes were significantly lower than for all other groups. The incidence of repeated rejection episodes in each patient was expressed by cumulative rates of acute rejection per patient per month. As expected, the incidence was low in patients undergoing transplantation for posthepatitic cirrhosis. The severity of these rejection episodes, as assessed by the need to receive rescue therapy, was also similar in both univariate analysis and cumulative rates.

Data from patients who had undergone liver transplantation for alcoholic cirrhosis were remarkably similar, with the exception of freedom from acute rejection, which was significantly lower for alcoholic patients.

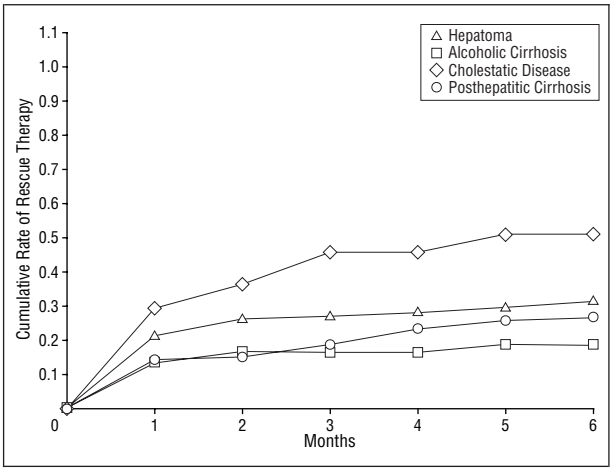

Figure 4. *Cumulative rates of rescue therapy per patient per month; patients undergoing transplantation for alcoholic cirrhosis vs posthepatitic cirrhosis vs hepatoma vs cholestatic disease.*

Patients who had undergone transplantation for alcoholic cirrhosis or posthepatitic cirrhosis were at reduced risk of acute rejection. The mechanisms responsible for this protection against rejection seem to differ in these 2 populations. The data do not support the hypothesis that this difference is simply related to a difference in the severity of cirrhosis at the time of transplantation or its nutritional consequence.

In the case of alcoholic cirrhosis, an inhibitory effect of alcohol on various aspects of the immune response appeared to be the most likely explanation and seemed to persist in the early postoperative period, despite abstinence from alcohol for several months before transplantation. The T-lymphocyte response to specific polyclonal activators may be severely impaired in alcohol abusers because of functional abnormalities in transmembrane signal-transduction pathways.[21] Futhermore, the function of macrophage Fc γ receptors is impaired specifically in correlation with the degree of liver insufficiency.[22] This impairment probably contributes to the high incidence of bacterial infections among such patients. In our analysis, however, the infection rate in patients with alcoholic cirrhosis was not different from those with other indications.

Patients who had undergone transplantation for posthepatitic cirrhosis were also at reduced risk for acute rejection and rescue therapy. The reason may be a peristent virus-induced defect in cell-mediated immunity.[23,24]

In contrast, patients who had undergone transplantation for cholestatic disease were at significantly increased risk for acute rejection and the need to receive rescue therapy. Both univariate analysis and cumulative rates showed the highest risk for acute rejection and for the need to receive rejection therapy. Even beyond the first month after liver transplantation, when the risk decreases significantly in all other groups, patients undergoing transplantation for cholestatic disease have rejection episodes requiring rescue therapy. The molecular genetics of these autoimmune liver diseases may influence the immune response to alloantigens through either direct T-cell interaction or through the influence of other closely linked genes.[25,26]

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The relevant observation of this study was the inclusion of patients who had undergone transplantation for hepatoma, in contrast to the publication of Farges et al.[13] During the observation period, none of the patients received chemotherapy. In our opinion, the risk of recurrence of disease is not an exclusion criterion for these patients, as the survival curve shows that 1-year survival is similar between the groups, and recurrence of disease or death usually occur after the first year. On the other hand, 84% of rejection episodes take place during the first month.

The incidence of acute rejection in patients with hepatoma was in a different proportion to the incidence of first acute rejection or first rescue therapy and cumulative rates of acute rejection episodes or rescue therapy. A rather low incidence of first acute rejection or rescue therapy was noted, similar to that in patients undergoing transplantation for alcoholic or posthepatitic cirrhosis. In contrast, a high rate of repeated acute rejection or repeated rescue therapy was observed in some patients. This resulted in an increased cumulative rate of acute rejection and cumulative rate of rescue therapy. The reason for this observation might be varying immunological behavior within this group of patients who had undergone transplantation for hepatoma. One explanation might be that patients with a high rate of acute rejection and subsequent rescue therapy have very powerful immune systems and do not suffer from recurrence of malignant neoplasms. Patients with recurrence of malignant neoplasms have immunological deficiencies and therefore are at low risk of acute rejection and receive no rescue therapy. The hypothesis could not be definitely confirmed by our data. Of the patients who died of malignant recurrence, 52% did not have any episodes of acute rejection and 76% never received rescue therapy. The samples in the subgroups were probably too small to reach statistical significance.

Multivariate analysis identified the underlying disease as a variable of independent prognostic significance for acute rejection and for the need to receive rescue therapy. Both our results and the investigations carried out on this subject indicate the importance of taking the original disease into consideration when choosing immunosuppressive therapy. All recipients receive the same initial therapy; however, beyond 3 months after transplantation we do not hesitate to reduce immunosuppression therapy significantly in the group at low risk for rejection.

Considering that significantly more patients die of infection than of acute or chronic rejection, we have to conclude that overimmunosuppression is common. On the other hand, of the patients surviving for more than 5 years after liver transplantation, more than 50% show significantly reduced renal function as an adverse effect of immunosuppressive therapy. In the light of these facts, additional investigations need to be carried out in the search for further appropriate parameters to make individually adjusted (reduced) immunosuppression possible in daily routine work.

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