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ORIGINAL ARTICLE

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transplantation for alcoholic cirrhosis

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Abstract In recent years, alcoholic cirrhosis has been accepted as an indication for OLT, compliance of patients suffering from alcoholic cirrhosis is still under discussion, however. 118 patients who had undergone OLT for alcoholic cirrhosis were considered for analysis. The mean follow-up time of the study population was 53.7 ± 38.9 months. Compliance was defined by 3 parameters: 1. Sobriety. Fifteen (13 %) out of 118 recipients suffered an alcohol relapse during the observation period. There was no difference between the groups with or without alcohol relapse concerning compliance with medication, incidence of rejection, or adherence to checkups. 2. Drug-compliance. Nineteen recipients (16 %) were not within the target range with the immunosuppressive medication. Comparison of the compliant- and non-compliant groups produced a significant difference for late acute rejection, the other parameters being similar in the subgroups. 3. Adherence to appointments. Nearly all patients in the study population (> 95 %) were compliant with both transplant and psychological appointments in the outpatient clinic. In conclusion, analysis of our data indicates that patients with OLT for alcoholic cirrhosis are compliant, although alcohol relapse occurs in 13 % of recipients.

Key words Alcoholic Cirrhosis · Liver transplantation · General compliance

Disagreement has existed as to whether liver transplantation (OLT) should be provided for patients with alcohol-induced cirrhosis. In recent years, alcoholic cirrhosis has been accepted as an indication for OLT. However, one of the major concerns with patients suffering from alcoholic cirrhosis, lack of compliance, is still under discussion. However, these concerns are based on assumptions rather than on data. The reason for this might lie in the small numbers of this population, as many centers have been reluctant to accept patients with alcoholic cirrhosis for OLT. For example, the porportion of OLT for alcoholic cirrhosis was 7.2 % of all adult OLT in the United States in 1987 [8]. Over the last few years, substantial evidence of successful outcomes and low graft rejection rates in patients receiving transplants for alcoholic cirrhosis has emerged. This has resulted in a growth in the amount of alcoholic cirrhotics undergoing OLT [3]. In contrast, the policy at our center has always been to treat alcoholism not as a patient's fault, but as a disease. If the underlying disease is cured, it is justifiable to treat the secondary complications, alcohol-induced liver cirrhosis, as well. Therefore, the proportion of OLT for alcoholic cirrhosis amounts to about 20 % of the transplant program at our center.

In a previous publication from our center [4] on the outcome of liver transplantation for alcoholic cirrhosis we analyzed 44 patients who underwent OLT for alcoholic cirrhosis from 1982 to 1993. Although alcoholic recidivism occured, it did not affect patient and graft survival. The outcome of these patients compared favour-

ably with that of patients with other chronic liver diseases. Furthermore, posttransplant social rehabilitation and compliance with immunosuppressive medication were excellent. However, despite general acceptance of alcoholic cirrhosis as an indication for liver transplantation, compliance of these patients is still under discussion. Therefore, data of a large, well documented study population were analyzed concerning this special issue.

The purpose of this retrospective study is to measure compliance by defined parameters. The outcome of OLT for alcoholic cirrhosis was assessed for each parameter of compliance and for general compliance.

Materials and methods

Study population

From January 1988 to January 1998, 168 patients underwent OLT for alcoholic cirrhosis at the Department of Transplant Surgery of the University of Vienna. For the purpose of this study, only patients who survived for more than 9 months and who were followed-up exclusively at our outpatient clinic, were considered, thus amounting to 118 patients for analysis. Data were retrieved from the electronical OLT database, where all medical records during hospital stay as well as records from the outpatient clinic were collected in a patient-based order. The diagnosis of alcoholic liver disease was based in each case on a history of habitual and excessive alcohol consumption, compatible clinical and laboratory findings, and morphology of the explanted diseased liver after tranplantation. Patients were generally considered for transplantation if liver function suggested a poor prognosis, corresponding to Child's score B or C. Contraindications included extrahepatic disease induced by alcohol. A determined period of abstinence from alcohol was not required, but most patients had ceased consuming alcohol at least 3 months prior to transplantation. Quantitative estimates of alcohol intake before surgery were not considered reliable. No formal psychiatric or psychological evaluation was performed until January 1993 (group 1, $n = 34$), although most patients suffering from alcoholic cirrhosis were examined at least once by a psychiatrist. During posttransplant follow-up repeated psychological examinations were carried out in all patients of group 1. In patients transplanted since 1993 (group 2, $n = 84$) the psychologist was also involved in pretransplant evaluation and selection of potential candidates. Additionally, CDT monitoring following OLT was introduced in January 1993.

For this study, compliance was defined by the following 3 parameters: sobriety, compliance with immunosuppressive medication, and adherence to check-up appointments. Furthermore, each of the 3 parameters consisted of 2 issues supporting each other, in order to increase reliability in the definition of general compliance. Sobriety and drug compliance permitted short-term as well as long-term valuation. Sobriety was ascertained by psychological examination (long-term valuation) and CDT (carbohydrate deficient transferrin) monitoring (short-term valuation), and drug compliance was indicated by incidence of late acute rejection (long-term valuation) and measurement of calcineurin-inhibitor blood levels (short-term valuation). Adherence to appointed check-ups were jugded separately for the transplant surgeon and the specialist psychologist.

1. Sobriety

The psychologist employed standardized questionnaires [2] and semi-structured interviews in order to classify drinking patterns and coping structures, as well as severity of somatic, psychological and social deterioration. The course between the visits was recorded retrospectively at the interview [1]. Alcohol relapse was defined as any exposure to alcohol at all. For the purposes of this study the quantity of alcohol was not considered reliable.

The psychological examinations were supported by routine measurement of CDT. The mechanism behind CDT formation may at least partly involve acetaldehyde-mediated inhibition of glycosyl-transferase, for which chronic alcohol consumption is a prerequisite [15, 23]. During alcohol abstinence, the CDT value normalizes with a half-life of 17 days [24]. The applied method for quantitative measurement of CDT is a commercially available double antibody radioimmunoassay (Pharmacia Diagnostics AB, Uppsala Sweden). The reference value amounts to less than 20 U/l for men and less than 26 U/l for women. CDT values were measured serially on a prospective basis.

2. Compliance with immunosuppresive medication

The long-term immunosuppressive regimen following OLT usually consisted in a calcineurin-inhibitor-based dual-therapy (either cyclosporin (CyA) or FK 506) with a low dose of prednisone of 2.5–5 mg/d. The calcineurin-inhibitors were adjusted to a whole blood trough level of 100–130 ng/l FPIA for CyA and 8–12 ng/l FPIA for FK 506, respectively. The target range was lowered in case adverse events occured with the drugs. Following an acute rejection episode receiving rescue therapy, azathioprine (1 mg/kg per d) or mycophenolate mofetil (2 g/d) were added for long-term immunosuppression. Whole blood trough levels of calcineurin-inhibitors were determined at each outpatient visit, routinely and on demand.

Any acute rejection episode after 3 months following transplantation and requiring rescue therapy was defined as a late acute rejection episode. Patients presenting with histological evidence of a rejection process > Grade 1 according to the Snoover [22] classification in the transplanted liver, as diagnosed by biopsy, underwent rescue therapy at our center. The rate of overall late acute rejection was calculated according to the Kaplan-Meier method and assessed as parameters for medication compliance.

3. Adherence to check-up appointments

Data concerning adherence to check-up appointments were collected from the computerized follow-up protocols of the study population. Appointments with transplant surgeons and with the psychologist were collected in one electronic database. Patients had frequent routine out-patient check-ups at which they were personally interviewed by a member of the transplant team. A complete laboratory investigation (hematology, liver parameters, coagulation, electrolytes, total protein, renal parameters, electrophoresis, lipid profile) as well as calcineurin-inhibitor whole blood trough levels, were determined at each visit. The follow-up intervals were usually once a week during the first month after leaving the hospital, twice a month during the second and third month, monthly during the first half-year, and every two or three months thereafter, regardless of the length of the observation period after the transplantation. A visit for any special problems was possible at any time. Appointments for psychological follow-up were arranged on the same date as those for surgical controls, usually in

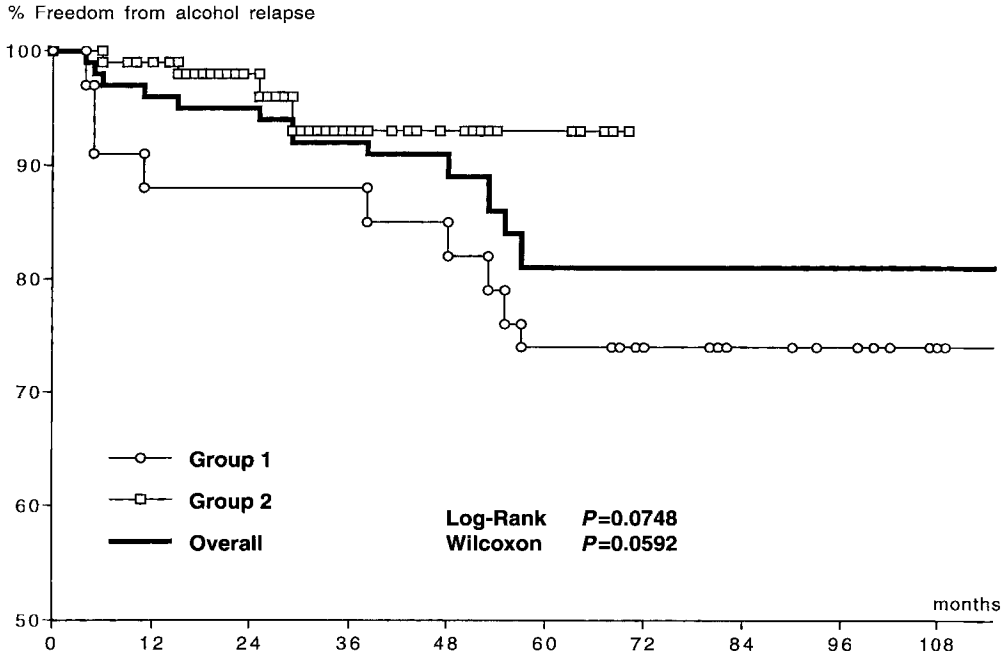

Fig. 1 Probability of freedom from alcohol relapse – overall relapse rate; group 1: patients undergoing transplantation before 1993 ($n = 34$) versus group 2: patients undergoing transplantation from 1993 ($n = 84$) to 1998

patients without drinking problems. As far as additional appointments were made, especially in patients who had suffered an alcohol relapse.

Statistical analysis

Freedom from late acute rejection and rate of alcohol relapse were calculated using the Kaplan-Meier method. The Log-Rank and Wilcoxon tests were applied to find differences between proportions and the significance of associations. Numerical data were compared using Student's t test. A probability value of $P < 0.05$ was considered to be significant. Analyses were performed up to January 1999. At that time, all of the 118 patients in the study population were available for follow-up.

Results

The mean follow-up period for the study population was 53.7 ± 38.9 months (range 9–179 months). Of 118 patients who were included in the analysis, 111 (94%) were alive in January 1999. All patients were followed by the outpatient clinic of our center for the whole observation period.

Alcohol relapse

In psychological examinations of 118 patients, 103 (87%) were found to have no problems with alcohol during the observation period and 15 (13%) had resumed alcohol consumption. Pretransplant evaluation by the psychologist and better patient selection permitted a reduction in the rate of alcohol relapse from 31% in the group undergoing transplantation before 1993 (mean follow-up 73.8 ± 46.3 months), to 5% in the latter group (mean follow-up 32.8 ± 18.4 months). The decrease in the alcohol relapse-rate over time indicated a trend but did not reach statistical significance (Log-Rank $P = 0.0748$, Wilcoxon $P = 0.0592$). Thus the overall relapse rate during the observation period was 13% (Fig. 1). A univariate analysis of the relapse rate was performed. The estimated risk for alcohol relapse after 1, 3, and 5 years was 4%, 9%, and 15%, respectively. One third of all recidivism events occurred during the first year after transplantation.

In the study population, 937 CDT measurements were performed prospectively (mean 7.9 ± 4.2 per patient). Compared with the psychological assessment, of the 15 patients who had suffered an alcohol relapse, 14 were detected by CDT and 1 was a false negative. However, 100 patients were truly negative and 3 showed false positive results. Hence a sensitivity of 93% and specificity of 97% were obtained. The subgroups with and without alcohol relapse did not differ (Table 1) with regards to their compliance with immunosuppressive medication ($P = 0.3787$), incidence of late acute rejection ($P = 0.4410$) or adherence to appointments ($P = 0.2536$).

Compliance with immunosuppressive regimen

In the study population, a total of 1998 whole blood trough-levels of calcineurin-inhibitors were measured. Eighty-eight patients (75%) received CyA, and a mean

Table 1 Compliance relating to alcohol relapse

$n = 118$	Alcohol relapse $n = 15$ (13%)	No alcohol relapse $n = 103$ (87%)	P-value
Drug non-compliant	2 (13%)	17 (17%)	0.3787
Late acute rejection	1 (7%)	8 (8%)	0.4410
Non-adherent to check-ups	0 (0%)	3 (3%)	0.2536

Table 2 Compliance relating to immunosuppressive therapy

$n = 118$	Drug compliant $n = 99$ (84%)	Drug non-compliant $n = 19$ (16%)	P-value
Alcohol relapse	13 (13%)	2 (11%)	0.3787
Late acute rejection	5 (5%)	4 (21%)	0.0079
Non-adherent to check-ups	2 (2%)	1 (5%)	0.2075

Table 3 Compliance relating to adherence to appointments

$n = 118$	Non-adherent $n = 3$ (3%)	Adherent $n = 115$ (97%)	P-value
Alcohol relapse	0 (0%)	15 (13%)	0.2536
Drug non-compliant	1 (33%)	18 (16%)	0.2075
Late acute rejection	0 (0%)	9 (8%)	0.3089

of 16.7 ± 5.4 measurements per patient were performed during the observation period. Compliance with medication was found in 75 patients (85%). Thirteen patients (15%) were not within the target range, in detail, 5% showed trough levels above and 10% below, respectively. Similar results were obtained in 30 patients (25%) receiving FK 506. 549 measurements were performed (mean 18.3 ± 4.7). Eighty per cent ($n = 24$) of these patients had trough levels within the target range, of the 20% ($n = 6$) who were non-compliant, 4% demonstrated levels above and 16% below the range.

Out of a total of 118 recipients, 19 were identified as being non-compliant with immunosuppressive therapy. Thus the incidence-rate of non-compliance in this sample was 16%. A comparison between the compliant and non-compliant subgroups revealed late acute rejection in 5% and 21%, respectively, a statistically significant difference ($P < 0.0079$). The two groups did not differ in terms of alcohol relapse or adherence to appointments (Table 2).

Out of 118 patients, 9 suffered late acute rejection during the observation period, an overall incidence of late acute rejection of 7%. The estimated risk at 1 and 5 years was 7% and 10%, respectively (Fig. 2). Of the 15 patients who returned to drink, 1 suffered a late acute rejection (11%). Fourteen patients (13%) with alcohol relapse did not show evidence of rejection. Therefore, in patients with alcohol relapse, the incidence of late acute rejection was not significantly different ($P = 0.4410$). None of the patients non-adherent to

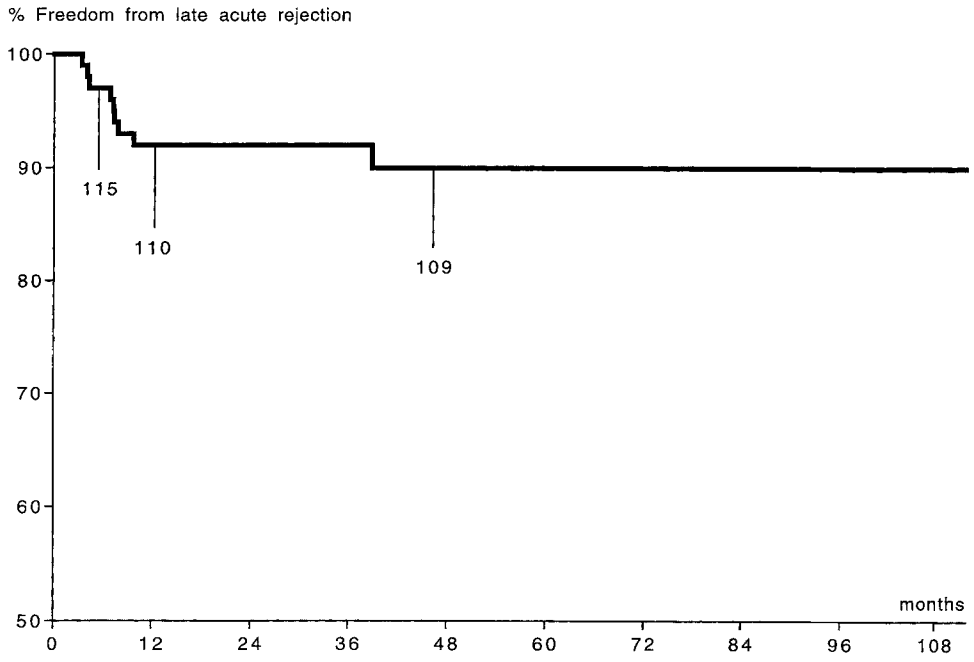

Fig. 2 Probability of freedom from late acute rejection. Numbers below the graph indicate patients at risk

check-up appointments had a late acute rejection ($P = 0.3089$). In patients who were non-compliant with immunosuppressive therapy, late acute rejection occurred in 44% of patients ($n = 4/9$) versus 14% ($n = 15/109$) who suffered no rejection. Therefore, the incidence of late acute rejection was significantly different ($P = 0.0079$).

Adherence to appointments

Of the 118 patients who were considered for study, none were lost for follow-up. Virtually all the patients of the study population (97%) were compliant with both transplant- and psychological appointments in the outpatient clinic. The proportion of additional psychological appointments with no check-up without transplant surgeon was 42%. Overall only 3 patients were found to be non-adherent to appointed dates for check-ups, they visited the outpatient clinic according to their private schedule or demand. One of these was non-adherent to transplant- as well as psychological appointments while the other two only missed psychological appointments. None of these 3 patients suffered from an alcohol relapse, and only one demonstrated non-compliance concerning immunosuppressive therapy.

The subgroups adherent and non-adherent to check-up did not differ (Table 3) concerning their rate of alcohol relapse ($P = 0.2536$), compliance with immunosuppressive medication ($P = 0.2075$) or incidence of late acute rejection ($P = 0.3089$).

Discussion

Due to the very inconstancy of human nature even in life-threatening or life-dependent situations, non-compliance will always be a problem. No gold standard exists for measuring compliance [7]. Most studies concentrate only on compliance with immunosuppressive medication and indicate predictors for drug non-compliance. Medication non-compliance has usually been documented by the finding of low cyclosporine levels [10]. Biological assays provide a direct measurement of medication intake but are limited by the half-lives of the drug. Thus, assay monitoring of calcineurin inhibitor blood levels only provides information about medication intake over the previous few days. Moreover, patients taking their medication correctly pending clinical visit can bias assay results and mask noncompliance [13]. Pill-count provides an indirect measurement of limited value because patients may fail to return unused pills or may deviate from dosage. Pill-counts usually overestimate compliance and do not allow detection of patterns of compliance behaviour. Electronic devices for measuring compliance behavior record the opening and closing times of the medication container, making it possible not only to detect patterns of compliance behavior, but also to count missed doses and to calculate time intervals between doses [7]. Although the electronic measurement has been described as the most reliable method of ascertaining non-compliance to date, it remains an indirect method [7]. Besides, electronic device monitoring is expensive and would not be paid for by health insurance. Detection of subclinical non-compliance with immunosuppressive therapy is even more difficult and can only be assessed by information on drug-taking behavior provided by the patient or family members [10, 17, 20]. The interview method has been described as a reliable method for non-compliance assessment, provided questions are asked in a non-threatening supportive manner [19, 20] by an independent investigator not belonging to the therapeutic team [16]. Unfortunately, the interview method does not reveal patterns of compliance behavior and has been found to underestimate the incidence of noncompliance [11]. The incidence of drug non-compliance is similar among kidney-, heart- and liver transplant recipients and seems to increase over time [9, 20, 21]. The prevalence of non-compliance in these populations is similar to non-compliance rates observed in other chronic disease states, e.g. hypertension or glaucoma [6].

The importance of medication compliance after organ transplantation is beyond dispute. Several authors have demonstrated non-compliance as being a major determinant of late graft failure [14, 10, 12, 17]. According to the results in the study presented, the rate of late acute rejection was significantly increased in patients who were drug non-compliant with immunosuppression. In contrast, in the drug-compliant and non-compliant subgroups there was no difference in respect of alcohol relapse rate or adherence to check-up appointments, either with the transplant surgeon or with the specialist psychologist.

In the study presented, analysis focused not only on compliance with the immunosuppressive therapy. Sobriety is also an important issue for compliance, especially in patients who have undergone OLT for alcoholic cirrhosis. In the past, the majority of transplant centers [18] have been reluctant to include these patients on the OLT waiting list because of a supposedly high rate of alcohol relapse which may potentiate poor compliance with the required immunosuppressive therapy. The overall alcohol relapse rate was 13% during the observation period. If the population is divided according to date of transplantation, a rather high relapse rate of 31% was found in the group who underwent transplantation before 1993. Two steps were observed in the alcohol relapse rate: during the first year posttransplant, and between the 3rd and 5th year after OLT. The first step occurred in patients, for whom the alcohol problem remained undetected before transplantation, based on in-

sufficient selection. The second step might be a result of inadequate psychological long-term follow-up. The reduction to 5% in the latter group was significantly affected by the pretransplant psychological evaluation and patient selection. In the posttransplant follow-up, the examinations performed by the specialist psychologist were supported by prospective CDT monitoring. Excellent sensitivity and specificity could be demonstrated [5], indicating reliable rates for alcohol relapse. CDT was reassesed frequently enough for monitoring of drinking behavior, as it can safely be stated impossible for patients suffering from alcohol relapse not to drink alcohol for 17 days (half-life of CDT) before a pending clinical visit. As expected from previous studies [4, 5] in patients without alcohol relapse versus those who suffered an alcohol relapse, no statistically significant difference could be demonstrated concerning the other two parameters of compliance. Patients who resumed alcohol consumption after OLT showed comparable drug compliance and adherence to check-up appointments to the subgroup without alcohol relapse.

The third parameter for the purpose of overall compliance was adherence to appointments for check-ups. It does not appear surprising that recipients keep appointments with transplant surgeons following such a radical event as an OLT. It could be argued that on the occasion of a surgical check-up, the patients have no alternative but to keep their psychological check-up appointments as well. In consideration of more than 40% additional appointments exclusively with the specialist psychologist, and the excellent adherence to these appointments, this argument must be disregarded.

A minority of patients was non-compliant concerning a single parameter. However, a correlation between drug non-compliance, alcohol relapse, or a failure to adhere to check-ups could not be demonstrated. Therefore, an overall non-compliant patient was not identified. It should be mentioned, that the number of patients being non-compliant in one of the three parameters was small and that therefore the power of statistics might be poor. On the other hand, it can be argued that small numbers of non-compliant patients implicate that most patients are compliant. Therefore, in spite of the limitations of statistics in this analysis, evidence of compliance appears to be established.

In summary, non-compliance with immunosuppressive medication was found in 16% of all patients and had a significant influence on late acute rejection. However, alcohol relapse (13%) did not show an effect on compliance with medication and did not increase the rate of late acute rejection. In conclusion, analysis of our data indicate that patients undergoing OLT for alcoholic cirrhosis are overall compliant, although alcohol relapse occurs in 13% of recipients.

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