Long-term medical complications and quality of life in adult recipients surviving 10 years or more after liver transplantation

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Abstract

Background and study aims : **Little information is available about long-term results after adult liver transplantation. This study analyses long-term medical complications, changes of immunosuppression, recurrence of primary disease and quality of life 10 years after liver transplantation.**

Material and methods : **During the period February 1984 – April 1994, 324 LT were performed in 282 adults (>15 years). One hundred forty-seven (52%) patients survived more than 10 years. Data regarding health status of 103 patients exclusively followed-up in our institution were analyzed.**

Results : **Actual 1, 5, 10 years survival rates of the 282 recipients were 76.6%, 64.9% and 52% respectively. Forty eight (46.6%) of the 103 studied patients had normal liver tests in their tenth year of the follow-up. Seventy-one (69%) patients were on a CyA, TAC or MMF monotherapy ; 31 (30%) patients had CyA levels of less than 100ng/ml. Forty five patients had recurrent allograft disease. Twenty-four (40.6%) of 59 liver biopsy available at 10th year were normal. Thirty five (34%) patients developed chronic renal failure ; nine (8.7%) of them had end-stage renal disease. New onset hypertension (> 140/100 mmHg) developed in 49 (47.6%) patients ; fourteen (13,6%) developed diabetes (glucose blood level > 140 mg/dl) and twenty five (24.2%) patients had serious cardiovascular events. Thirteen (12.6%) patients had a BMI>28 and thirty six (35%) patients had elevated serum cholesterol (> 220 mg/dl). Cataract was present in 8 (7,7%) patients. De novo malignancy developed in 23 (22.3%) patients. One patient each developed nasopharyngeal lymphoproliferative disease and myeloma. Quality of life of this patient cohort was excellent as shown by a Karnofsky score of more than 80% in 96.6% of patients.**

Conclusion : **The high rate of medical complications and especially of malignant tumours in this long-term follow-up study indicate that further optimization and especially minimization of immunosuppressive therapy as well as development of newer therapies in order to prevent recurrent allograft diseases are the priority for the future development of transplant medicine.** (Acta gastroenterol. belg., **2005**, 68, **323-330**).

Key words : liver transplantation, long term results, immunosuppression, recurrent disease, tumor, quality of life.

Abbreviations

AST/ALT : aspartate/alanine aminotransferase
AZA : azathioprine
BMI : body mass index
CyA : cyclosporine A
CNI : calcineurin inhibitors
CrCl : creatinin clearance
CRF : chronic renal failure
GGT : gamma-glutamyl-transferase
HBV : hepatitis B virus, HCV : hepatitis C virus
IS : immunosuppression
Ksc : Karnofsky score
LDST : low -dose steroid
(O)LT : (orthotopic) liver transplantation
MMF : mofetil mycophenolate
MP : methylprednisolone
PBC : primary biliary cirrhosis
PTDM : posttransplant diabetes mellitus
PTLD : post transplant lymphoproliferative disease
TAC : tacrolimus
WHO : world health organization

Introduction

Orthotopic liver transplantation (LT) has become a routine therapy for end-stage, irreversible, acute or chronic liver disease, liver based metabolic diseases and selected hepatobiliary malignancies. Results have improved greatly since the introduction of calcineurin inhibitors and the refinement of surgical techniques (1,2,3). There have been numerous reports on short-term outcome after LT, however little information is available in relation to long-term results.

This study analyses long-term medical complications, changes in immunosuppression, recurrent disease and quality of life in 103 adult recipients survived more then 10 years after allograft LT and who were followed-up completely in our transplant unit.

Material and methods

During the period February 1984 – April 1994, 324 LT were performed in 282 adults (> 15 years of age) at Cliniques St. Luc. 147 (52%) of them survived more than 10 years. One patient had combined liver-pancreas and two had combined liver-kidney transplantation. Data regarding health status of 103 patients exclusively followed-up in our institution were analyzed. Forty-four patients, followed in other transplant centers, were excluded from this analysis.

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Table 1. — **Primary indications for liver transplantation in the 103 studied adult patients followed up to 10 years. Emergency LT is indicated within brackets**

Diagnosis	N patients
Primary biliary cirrhosis	20
Sclerosing cholangitis	4
Viral hepatitis C	15
B	4 (4)
B + C	1
B + D	8
Alcoholic cirrhosis	9
Autoimmune hepatitis	4 (1)
Cryptogenic	6
Wilson disease	1(1)
Malignancy	8 *
Others	17

* Three other patients had incidental hepatocellular cancer.

Indications for LT in the studied patient group are listed in Table 1. Mean age at time of first LT of these 56 men and 47 women was 44.7 ± 12.6 years.

Fourteen (13.6%) patients were retransplanted ; ten of them within the first post-LT year because of primary graft dysfunction (5×), chronic rejection (2×), biliary complication (2×) and bleeding (1×). One patient had re-LT after 19 months because of chronic rejection, one after 29 months because of ischemic type biliary tract lesions (ITBL), one after 7 years because of *de novo* HCV cirrhosis and one after 13 years because of recurrent primary biliary cirrhosis (PBC).

All hospitalization and outpatient charts were retrospectively reviewed. Date of LT and of death, body mass index (BMI), creatinin clearance (CrCl), liver tests (bilirubin, ALT, GGT), blood glucose and serum cholesterol levels, immunosuppressive regimen, cyclosporine or tacrolimus dose (per kg) and dosage (through blood level), diabetes mellitus, arterial hypertension, osteoporosis, malignancy, cardiovascular events, hyperlipidemia and any other pathology were recorded.

Arterial hypertension was defined following WHO criteria as a systolic blood pressure > 140 mmHg and diastolic blood pressure > 100 mmHg. Hyperlipidemia was defined as fasting total serum cholesterol > 220 mg/dL and diabetes mellitus as fasting plasma glucose > 140 mg/dL on at least two separate occasions. Overweight was defined in men as BMI over 27.8 kg/m^2 and obesity as BMI > 31.1 kg/m^2 ; in women these values were 27.3 kg/m^2 and 32.3 kg/m^2 (4).

Creatinine clearance (CrCl) was estimated using Cockroft formula. Renal insufficiency was defined as CrCl < 75 ml/min standardized to a body surface area of 1.73 m^3 (corresponding to CrCl of 43.35 ml/min/m^2) (5).

Osteoporosis was diagnosed when back or articular pain became evident in presence of radiological signs of bone loss or compression fracture or when bone density was > -2.5 Z- score on densitometry (6).

Protocol liver biopsies were carried out 1, 3, 5, 7 and 10 years post-LT and when indicated. All patients had at least 3, 5 or 10 year biopsies.

Immunosuppression (IS) varied over the studied time period. Between 1984-1988 IS consisted of cyclosporine A - based (CyA) – (Sandimmun,-Novartis-Basel-CH), metylprednisolone (MP), azathioprine (AZA) and monoclonal (OKT3-Orthoclone,-New Jersey- USA) or polyclonal (ALS or R-ATG,-Fresenius-Homburg-G) or the locally produced anti-IL-2-receptor (Lo-Tact) antibodies. From 1989 to 1990, a prospective randomized study was done comparing quadruple IS, using OKT3 or Lo-Tact, to triple immunosuppression (7). Between 1991 and 1994 CyA-based triple drug IS was prospectively compared to CyA-based low-dose steroid (LDST) triple drug therapy. Patients with stable graft function and CyA dosage were offered steroid withdrawal from the third month post-LT onwards (8).

Treatment of acute rejection was based on clinical, biochemical and/or histopathological findings. Before introduction of LDST, rejection treatment consisted of several boluses of MP (up to 6,5 g). Corticosteroid-resistant rejection was treated with 10 to 14 day course of OKT3 or R-ATG. Since introduction of LDST IS, rejection has been treated with much lower doses (0,6 to 1 g) of MP ; in case of corticosteroid-resistant rejection, a 10 days course of OKT3 was given.

Ten patients were switched to Tacrolimus (TAC), due to delayed chronic (6×) and acute rejection (4×).

Since 1988 antimicrobial chemoprophylaxis was standardized, consisting of temocillin and oxacillin for elective patients and of ceftazidim and vancomycin for high risk patients (emergency and haemorrhagic transplants).

Since 1990 viral prophylaxis consisted of acyclovir or sequential iv/po gancyclovir administration for 4 months. Fungal prophylaxis consisted of a 10 day course of low dose (10 mg) amphotericine B and protozoal prophylaxis consisted of trimethoprim- sulfamethoxazole, three times a week, until monotherapy CNI was reached.

Since 1989 HBV infected patients were treated, from the anhepatic phase onwards, with high doses of specific anti-HBS immunoglobulins (Hepacaf,-CAF-Red Cross-Belgium) in order to obtain protective anti-HBS antibody levels above 200 mUI/ml.

Quality of life was assessed annually according to the Karnofsky Performance Score (KSc). Scores from 80-100 represent ability to carry out normal work and activity ; scores from 50 to 70 represent ability to care for personal needs but with varying amounts of assistance and inability to work (unable) ; scores 0 to 40 defined patients unable to care for themselves and needing chronic assistance (disabled) (9).

Following the practice of the European Liver Transplant Registry (ELTR) early and late deaths or events were classified as those occurring within or after the first 3 post – LT months.

Table 2. — **Causes of late death in 282 adult recipients transplanted during the studied follow-up period**

Cause of death	Delay LT- dead			
	3 mo - 1yr	*1-5yrs*	*5-10yrs*	*Total*
Sepsis/MOF	5	2	6	13
De novo tumor		2	4	6
PTLD	1		1	2
Recurrent tumor	5	13	4	22
Recurrent viral disease	3	8	5	16
De novo HCV			2	2
Cerebral bleeding	2		4	6
Cardiovascular disease	2	3	2	7
Chronic rejection	1	2		3
Suicide		1	1	2
Other		1	7	8
Total	19	32	36	87

Results

Survival rates

Actual survival rates at 1, 3, 5, 7, 10 years of the 282 patients transplanted between 1984 and April 1994 were 76.6%, 69.1%, 64.9%, 61,3% and 52% respectively.

The longest surviving patient is now 19.5 years post-LT. One hundred thirty one (47.8%) patients died during the follow up period, 45 (16%) of them within the first 3 post-LT months.

The causes of 87 late (> 3 months) deaths after LT are shown in Table 2.

Ten (9,7%) of the 103 studied recipients died after 10 years due to de novo allograft HCV infection (2x : 15,6 and 16y), recurrent HCV infection (2x : 10,9 and 12,3y), trauma (2x : 11,8 and 16y), colon cancer (1x : 13,7y), myocardial infarction (1x : 12,8y) and peritonitis due to inflammatory bowel disease (1x : 12,5y). One patient died during re-LT, done because of recurrent PBC, 13 years after the first LT. Four patients were retransplanted at other transplant centers because of recurrent PBC (1x : 12y) and HCV cirrhosis (3x : 12,13,16y).

Immunosuppression

The variation of immunosuppressive regimen during the studied period is shown in Table 3. The overall tendency was to diminish as well number of drugs as their respective dosages. Steroids and AZA were systematically withdrawn if possible (Fig. 1). After ten years, 71 (69%) of patients were on CyA, TAC or MMF monotherapy ; 31 (30%) patients had through CsA levels < 100 ng/ml.

Two (1.9%) patients have an excellent biochemical and clinical evolution without any IS. Three (2.9%) patients presented delayed acute rejection, due to IS stop in two of them [(because of non compliance (1×) and of myeloma (1×)] ; their evolution was good after resuming IS.

Protocol liver biopsies revealed chronic rejection in 5 (4.8%) patients. Three patients were switched to TAC or MMF, one patient was retransplanted 15 years after the first LT and one patient is waiting for reLT.

Liver tests

Ten years after LT, 48 (46.6%) patients had normal liver tests. Two patients had elevated bilirubin due to Gilbert syndrome. Evolution of bilirubin, ALT and GGT levels are shown in Fig. 2.

Mean GGT values decreased during the first five years but afterwards slowly increased, due to primary disease recurrence [present in 35 (34%) patients] and/or biliary complications [present in 16 (15,5%) patients]. Six patients had cholangitis caused by bile duct stones 1, 6, 9, 10, 16 and 18 years post-LT. One of them required hepaticojejunostomy at 10 and 18 years post-LT ; five patients were treated endoscopically. Six patients had delayed endoscopic biliary stenting because of stenosis. One patient required endoscopic papillotomy 10 years after LT because of stenosis of the sphincter of Oddi and one patient required endoscopic resection of malignant ampulloma 16 years after LT. One patient had severe cholestasis due to recurrent PBC 11 years after LT and one patient is waiting for re-LT because of chronic rejection, 13 years after the LT.

Recurrent disease

Fifteen (93.7%) of the16 patients grafted because of HCV cirrhosis had histologically proven recurrent viral disease. All but two were alive10 years after LT. One died 14 years post LT because of myocardial infarction and one died because of sepsis 10 years after LT. Two (12.5%) of 16 HBV-patients had normal 10 year liver biopsy, three (18.7%) had chronic B hepatitis ; two had

Table 3. — **Evolution of immunosuppression during the studied 10 years post-LT follow-up period**

F-up	*CyA/Cs*/Aza		*CyA*/Aza		*CyA/Cs*		*CyA/MMF*		*CyA-MONO*		*TAC/Cs*		*TAC – MONO*		*TAC/MMF*		*AZA-MONO*		*MMF-MONO*	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1 y	60	66	0		25	28	0		0		5	5,5			0		0		0	
3 y	24	26,6	7	7,8	33	36,6	0		20	22,2	1	1,1	5	5,5	0		0		0	
5 y	11	12,2	11	12,2	29	32,2	0		31	34,4	1	1,1	7	7,8	2	2,2	0		0	
7 y	7	7,7	11	12	13	14,4	1	1,1	47	52,2	1	1,1	7	7,8	2	2,2	1	1,1	0	
10 y	2	2,2	7	7,8	7	7,8	1	1,1	61	67,8	1	1,1	8	8,9	1	1,1	1	1,1	1	1,1

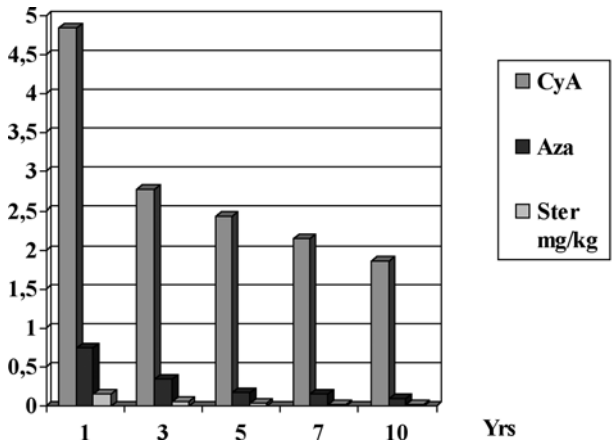


Fig. 1. — Evolution of doses of immunosuppressive drugs during the 10 years post-LT follow-up period.

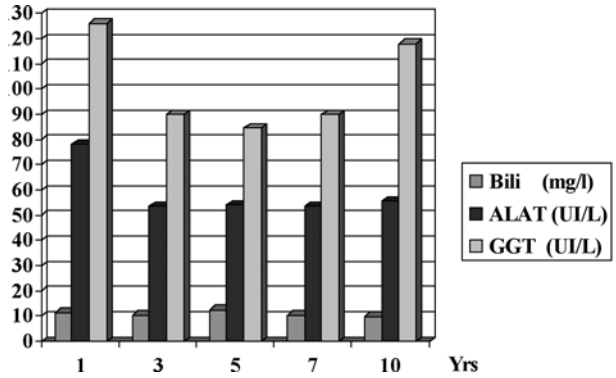


Fig. 2. — Evolution of liver tests during the 10 years follow-up period.

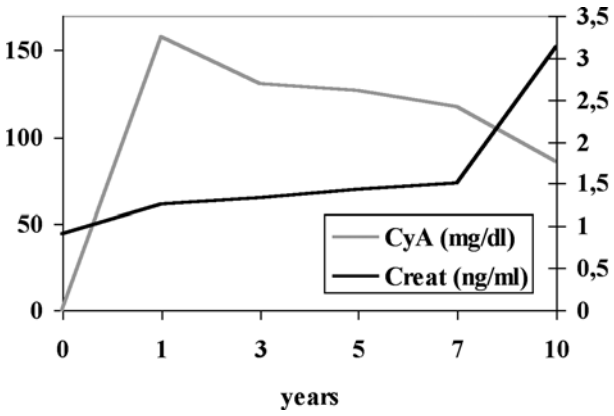
aspecific hepatitis. Three patients transplanted because of B - D cirrhosis developed *de novo* C hepatitis ; one of them required re-LT 4 years later. No biopsies were available in the remaining six patients.

Fourteen of 20 PBC patients had normal liver tests. Despite absence of cholestasis, histological recurrence was documented in 7 (70%) of 10 available 10 years biopsies. One patient with primary sclerosing cholangitis had biopsy proven recurrence ; a second patient had chronic active HCV hepatitis.

Three (33%) of nine alcoholic patients admitted renewed alcohol use after LT. Two died 12 and 14 years post LT due to trauma, one developed hepatitis C allograft cirrhosis. Five severely obese patients (BMI range from 34,2 to 40) had slightly elevated ALT and GGT related to steatosis.

One patient transplanted for autoimmune cirrhosis died 13 years after LT due to complicated ulcerative colitis ; she had normal liver tests. Two other patients had recurrent disease with biopsy proven fibrosis.

One patient with Wilson disease had a normal liver biopsy, a second one died 15 years post- LT due to a HCV allograft cirrhosis.



* Hemodialysis and renal transplantation are capped at 4 mg/dl creatinine value.

Fig. 3. — Relation between serum creatinin level and CyA trough levels during the 10 years follow-up period.

There was no tumor recurrence in the 8 patients surviving 10 years after LT done because of hepatocellular cancer (9×) and cholangiocarcinoma (1×). One patient who presented breast localization of epithelioid hemangioendothelioma 7 years after LT remains in good condition 14 years post- LT.

Medical complications

Renal disease

Serum creatinine rose progressively during the study period despite lowering of CyA dosing (Fig. 3). Three (3.3%) patients had chronic renal failure(CRF) before LT. Mean estimated pre-LT CrCl was 99,4 ± 39 ml/min/m^2. Six patients required postoperative hemodialysis because of acute renal failure ; one of them developed CRF. During the first post-LT year CrCl decreased to 68,8 ± 30 ml/min/m^2. Seventeen (18.8%) patients developed CRF. The incidence of CRF, defined as CrCl of 43.35 ml/min/m^2) rose to 20% (18 pat) in third year, 23.2% (21 pat) in fifth year and 34% (35 pat) in the tenth post-LT year. During the follow-up period 9 (8.7%) patients had irreversible end-stage renal disease ; six patients are hemodialyzed and three patients had a kidney transplant at 9 (2×) and 17 years after LT.

Five (4,8%) patients had hyperuricemia (> 9 mg/dl) requiring medical treatment.

Diabetes mellitus

Nine (8.7%) patients had preexisting diabetes mellitus ; 7 of them were insulinodependent. Fourteen (13.6%) recipients developed *de-novo* post-LT diabetes ; seven of them were insulinodependent. In three insulinodependent patients, insulin could be withdrawn rapidly following steroid withdrawal.

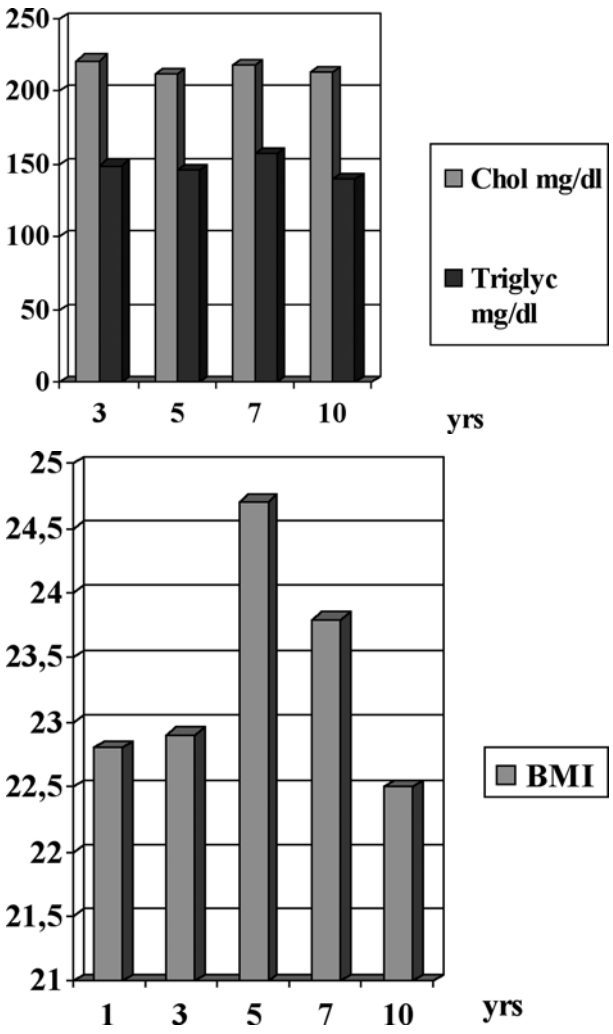


Fig. 4. — Evolution of cholesterol, triglycerids and BMI during the 10 years post-LT follow-up period.

Arterial hypertension

Pre-LT hypertension was present in 17 patients (16.5%) ; two needed double drug therapy. New onset hypertension developed in 49 (47.6%) patients. Thirty-three patients required single drug, 8 patients double, 7 patients triple and one patient quadruple drug therapy. Three of them were able to discontinue their antihypertensive medications one, two and four years post-LT.

Calcium channel blockers were prescribed in 47 patients.

Renal artery stenosis, diagnosed three times, was successfully treated twice using percutaneous angioplasty ; one patient needed renal transplantation.

Cardiovascular complications

Twenty-five (24,2%) patients sustained de novo cardiovascular events. Two patients required cardiac revascularisation, one patient each needed femoro-popliteal bypass and iliac- aortic bypass. One patient had myocardial infarction, two patients presented arythmia, one patient had congestive heart failure ; one patient had significant carotid stenosis, four patients had stroke and two patients had transient ischemic attack. The mean age of these patients at onset of their cardiovascular events was 62 years.

Hypercholesterolemia

Pre-LT mean serum cholesterol levels, available in 45 patients was 158.9 ± 80,47 mg/dl. Post-LT mean cholesterol level rose to 221,8 ± 63,4 mg/dl in the third post-LT year, afterwards values slowly decreased to 211.73 ± 45 mg/dl in the fifth, 217.61 ± 48 mg/dl in the seventh and 213.87 ± 51 mg/dl in the tenth post-LT year (Fig. 4). These changes paralleled the reduction of IS and especially of steroids.

Overall, 36 (35%) patients had elevated serum cholesterol levels ; seven required statin treatment using HMG-CoA reductase inhibitors.

Body weight

Mean BMI increased from 22,86 kg/m^2 pre-LT to 24,75 kg/m^2 in fifth post-LT year, afterwards these values decreased to 22,5 kg/m^2 at the tenth post-LT year (Fig. 4). These modifications went together with the reduction of steroid dosing.

Ten years post-LT 13 (12.6%) patients were overweighted (BMI > 28) ; ten moderately and three severely. In the obese pre-LT group 7 patients lost weight and normalized their BMI after LT, 3 kept an identical weight and 5 increased their weight.

Osteoporosis

Twenty three (22.3%) patients, 14 of whom were female, had osteoporosis. Ten patients (6 females and 4 males) developed spontaneous fractures. Seven patients had severe pre-LT osteoporosis. One patient had avascular femoral head necrosis.

Cataract

Cataract was present in 8 (7.7%) patients. Three patients had diabetes mellitus, one patient end-stage renal failure and two patients had long-term pretransplant steroid therapy. All patients had received high doses of MP to treat acute rejection.

One primary sclerosing cholangitis patient developed chorioretinitis.

Neurological disorders

Apart from cerebral vascular events in 5 patients, four patients developed polyneuropathy. One patient had centropontine myelinolysis and one patient had leucoencephalopathy.

Malignancy

De novo malignancy was present in 23 (22,3%) patients. Median time to diagnosis was 8,7 years after

LT (range 3 to 13). The most common malignancy was skin cancer : all five basal cell and two spinocellular cancer lesions could be locally excised. Nasopharyngeal lymphoproliferative disease developed once three years after LT ; remission was achieved after radiotherapy and IS withdrawal. Epiglottic cancer was diagnosed in one patient 6 years after LT, done because of fulminant B hepatitis and one oropharyngeal cancer developed 8 years post- LT, done for alcoholic cirrhosis. The former patient had laryngectomy, the latter radiotherapy followed by pharyngectomy and lymphadenectomy 5 years later because of tumor recurrence.

Colorectal cancer was diagnosed three times ; one patient died 14 years post-LT because of liver metastasis. Three females patients developed breast cancer and two males had prostate cancer. Myeloma and renal cancer were diagnosed each once.

Quality of life

The Karnofsky score (KSc) after 10 years was more than 80 in 96.6% of the survivors. Fifty one (49.5%) patients had a 100 KSc. Thirty recipients had normal activity with mild disturbances (90 KSc) and six had 80 KSc (normal activity with fatigue). The lower KSc were due to graft problems (recurrent disease, de novo viral infection, chronic rejection), cardiovascular complications, neurological disease, severe osteoporosis and obesity. Three (3%) patients had a 70 KSc due to rheumatoid arthritis (1) and chronic renal failure requiring hemodialysis (2).

Five patients had a normal pregnancy with normal delivery 1 (2), 2, 3 and 4 years post-LT. All children developed harmoniously without congenital abnormalities.

Discussion

Liver transplantation should allow the recipient to return to a normal life, including all its psychological and social aspects. Most transplant centers evaluate their results in terms of patient and graft survival and focus on early complications and short-term results. Few reports address long-term results after adult LT (10,11).

Steroid withdrawal after adult LT reduces well known complications of its usage such as diabetes, obesity, hypertension, bone disease. Steroids can be safely withdrawn in 68-100% of LT patients and CsA monotherapy can be obtained in 21,4% to 93% patients (12-13). The patients followed in this study underwent LT during the eighties and beginning of the nineties when only few immunosuppressive drugs were available and when there was a tendency to maintain higher doses of immunosuppressive agents. Steroid withdrawal in these patients was started in the early nineties. The effects of this policy are clearly shown on the evolution of BMI, weight and cholesterol levels. More than two-third of recipients were on CyA or TAC monotherapy, half of them had even low levels of CyA. Incidence (2,9%) of late onset acute rejection was low and so the incidence of chronic rejection (4.8%). These results are in contrast to the much higher rates (21 to 23%) of late acute cellular rejection reported by Wiesner and Ramji (14,15). A trend towards increased chronic rejection has been reported in patients who developed late acute rejection (15).

Recurrent allograft disease is of major concern during long-term follow-up of liver transplanted patients. Indeed 35% of our long-term survivors have histologically proven recurrent primary disease. *Recurrent* viral HCV, reported in 70% to 100% of patients, is the most frequent problem (16). Fortunately, HBV immunoprophylaxis using long-life specific anti-HBs antibodies allows to reduce substantially or even eliminate HBV allograft reinfection (17,18). Cholestatic autoimmune liver diseases such as primary sclerosing cholangitis, primary biliary cirrhosis and autoimmune hepatitis recur frequently (10 to 20% of patients) (19,20). Most of the documented PBC recurrences keep a favorable and slow biochemical and clinical evolution.

Hyperlipidemia, obesity, arterial hypertension and diabetes mellitus are established risk factors for cardiovascular disease (21). Mortality due to cardiovascular disease in LT accounts for 5% to 10% but is about 3-5 times lower than in other solid organ transplantations. This may partly be explained by a lower risk of hyperlipidemia after LT. Indeed elevated serum lipids have been reported in more than 60% of heart or kidney in comparison to 30% incidence in LT recipients (22,23). Sheiner reported no statistically significant prevalence of cardiovascular disease in liver recipients surviving $\geq$ 5 years in comparison with U.S. adult population. More and more frequent acceptance of elderly recipients with associated diseases predisposes to atherosclerotic vasculopathy and may therefore increase in the future the prevalence of post-LT cardiovascular disease (6).

Calcineurin inhibitors and corticosteroids are factors known to cause arterial hypertension apart from renal artery stenosis, nephropathy and obesity (24). Lower incidences of post-transplant hypertension have been reported with TAC in comparison to CsA, probably related to the more frequently associated steroid-sparing regimen (25). Multifactorial pathogenesis makes post-transplant hypertension the most common complication in liver recipients, ranging from 65 to 85% (26). Calcium channel antagonists and angiotensin-converting enzyme inhibitors are the drugs of choice, being even capable to reduce CNI induced nephrotoxity (27). Angiotensin-converting enzyme inhibitors may prevent or slow- down the development of heart failure with left ventricular dysfunction, reduce mortality following myocardial infarction and also prolong survival of patients with heart failure.

The incidence of posttransplant diabetes mellitus (PTDM) is present in 4 to 20% of transplant recipients and it may result in morbidity due to micro- and

macrovascular complications. Most patients develop PTDM within the first three months. Corticosteroids cause PTDM in a dose-dependent manner, primarily by inducing insulin resistance (28). CNI cause PTDM in a multifactorial way. CsA can cause a direct toxic effect on pancreatic β-cells, TAC is responsible for morphological damage and impaired insulin synthesis and secretion. The diabetogenic side effect of TAC appears to be dose related and b-cells damage may be reversible. Management of PTDM includes steroid withdrawal and initiation of insulin or oral hypoglycemic drug therapy.

CRF (GFR < 29 ml/min/1.73 m^2) is a common complication of LT, affecting up to 18% of patients within five years after transplantation (29). The risk of CRF is higher among liver transplants recipients under CyA – based IS. Up to 9,5% of patients develop end-stage renal failure (30). Both numbers correspond with the findings in this follow-up study.

Delayed reduction of CNI rarely result in significant improvement of renal function as exemplified in our series. It will therefore be necessary to switch the successfully transplanted patients early during the follow-up period to CNI-free IS (29).

Osteoporosis is a well recognized complication of organ transplantation. Corticosteroids and cholestatic liver disease clearly increase the risk of bone loss. CyA also seems to contribute to this complication. The Incidence of the post-LT osteoporosis in this study is equal to the incidence (27%) reported by Kizilisik in a 10 year survival group about (31). Adapted physical activity, hormone replacement therapy in post-menopausal women and administration of biphosphonates can increase bone mineral density (32).

The high incidence of all kinds *de novo malignancy* after LT, confirmed again in these series, is of great concern for all allograft recipients (33). Reported tumor incidence reaches 12% of LT recipients. About 2% of adult liver recipients develop post-transplant lymphoproliferative disease (PTLD). The greatest risk factor for its development is the heaviness of IS. The treatment consists in a reduction or even withdrawal of IS. Chemotherapy may be necessary but may increase the high incidence of infectious complications (34). Incidence of PTLD and non-melanoma skin cancer is significantly higher in liver recipients compared with non-transplanted population.

LT usually leads to a marked improvement of *quality of life* as shown in many studies (35-37). Impressive improvements of Karnofsky score are already reported at the end of the first post-transplant year and improvement of quality of life is generally better in liver recipients than in other solid organ recipients (38). Despite the fact that liver recipients significantly improve their perception of health status, self-image and ability to function from the first post-LT year onwards, they do not reach the same level as the general population (39). They keep a prevalence to psychiatric morbidity comparable with that of general medical patients. Anxiety, depressive and organic mood disorders are more common comparing to a normal, healthy population. Apart from their psychological problems of accepting dependence on drugs and on medical staff and apart from problems with the social and professional settings, the awareness of recurrent allograft disease is a major cause of psychological distress. Especially HCV reinfection is associated with significantly greater depression, (phobic) anxiety, and paranoid ideation (40). Hilbrands investigated the effect of immunosuppressive drugs on quality of life in kidney recipients. Their data suggest that CNI monotherapy may lead to a higher degree of psychosocial well-being and that impaired quality of life is mostly related to steroid use (41).

The near normal lifestyle of young female recipients was accompanied by a desire to procreate despite awareness of side effects of long-term IS.

In conclusion major progress has been made in the field of LT since the NIH Consensus Development Conference of 1983. Nevertheless a majority of adult liver recipients experience side-effects and complications essentially related to long-term immunosuppressive therapy and recurrence of allograft disease. The challenge of all transplant teams will consist of developing minimized or even better tolerated immunosuppressive strategies in the near future.

References

1. STARZL T.E., DEMETRIS A.J. Liver Transplantation – Year Book Med Pub, Chicago, 1994.
2. LERUT J., MOLLE G., DONATACCIO M. *et al*. Cavocaval liver transplantation without venovenous bypass and without temporary portocaval shunting : the ideal technique for adult liver grafting ? *Transplant. Int*., 1997, **10** : 171.
3. O'GRADY J.G., BURROUGHS A., HARDY P. *et al*. Tacrolimus versus microemulsified ciclosporin in liver transplantation : the TMC randomised controlled trial. *Lancet*, 2002, **360** : 1119-25.
4. NAJJAR M.F., ROWLAND M. Anthropometrics reference data and prevalence of overweight among United States : 1976-80. *Vital Health Stat*., 1987, **11** : 238.
5. COCKROFT D.W., GAULT M.H. Prediction of creatinine clearance from serum creatinine. *Nephron*., 1976, **16** : 31.
6. SHEINER P.A., MAGLIOCCA J.F., BODIAN C.A. *et al*. Long-term medical complications in patients surviving more than 5 years after liver transplant. *Transplantation*, 2000, **69** : 781-789.
7. REDING R., FEYAERTS A., VRAUX H. *et al*. Prophylactic immunosuppression with anti-interleukin-2 receptor monoclonal antibody Lo-Tact-1 versus OKT3 in liver allografting. A two year follow-up study. *Transplantation*, 1996, **61** : 1406-1409.
8. LERUT J. CICCARELLI O., MAUEL E. *et al*. Adult liver transplantation and steroid-azathioprine withdrawal in cyclosporine (Sandimmun) – based immunosuppression. 5 year results of a prospective study. *Transpl. Int*. 2001, **14** : 420-428.
9. GRIECO A., LONG C. Investigation of Karnofsky Performance Status is a measure of quality of life. *Health Psychol*., 1984, **3** : 129-142.
10. SHARON W.D. Quality-of-life assessment : recent trends in surgery. *CJS* 1996, **39** : 368-372.
11. LERUT J., MATTHYS J., LEMAIRE J., VAN THUYNE V., CICCARELLI O., GOFFETTE P. *et al*. Adult liver transplantation at UCL : update 2002. *Acta Gastroenterol. Belg*., 2004, **67** : 188-196.
12. LERUT J.P. Avoiding steroids in solid organ transplantation. *Transpl. Int.*, 2003, **61** : 213-224.
13. STEGAL K.D., EVERSON G.T., SCHROTER G. *et al*. Prednisone withdrawal late adult liver transplantation reduces diabetes, hypertension, and hypercholesterolemia without causing graft loss. *Hepatology*, 1997, **25** : 173-177.

14. WIESNER M.H., GOLDSTEIN R.M., DONOVAN J.P. *et al*. The impact of cyclosporine dose and level on acute rejection and patient and graft survival in liver transplant recipients. *Liver Transpl. Surg.*, 1998, **4** : 34-41.
15. RAMJI A., YOSHIDA E.M., BAIN V.G. *et al*. Late acute rejection after liver transplantation : the Western Canada experience. *Liver Transpl.*, 2002, **8** : 945-51.
16. BERENGUER M., PRIETO M., PALAU A. *et al*. Recurrent hepatitis C genotype 1b following liver transplantation : treatment with combination interferon–ribavirin therapy. *Eur. J. Gastroenterol. Hepatol.*, 2004 Nov, **16** : 1207-12.
17. SAMUEL D. Liver transplantation and hepatitis B virus infection : the situation seems to be under control, but the virus is still there. *J. Hepatol*., 2001, **34** : 943.
18. STEINMULLER T., SEEHOFER D., RAYES N. *et al*. Increasing applicability of liver transplantation for patients with hepatitis B-related liver disease. *Hepatology*, 2002, **35** : 1528-35.
19. GRAZIADEI I.W., WIESNER R.H., MAROTTA P.J. *et al*. Long-term results of patients undergoing liver transplantation for primary sclerosing cholangitis. *Hepatology*, 1999, **30** : 1121-7.
20. RATZIU V., SAMUEL D., SABAGH M. Long-term follow-up for autoimmune hepatitis : evidence of recurrence of primary disease. *J. Hepatol*, 1999, **30** : 131-141.
21. RABKIN J.M., CORLESS C.L., ROSEN H.R. *et al*. Immunosuppression impact on long-term cardiovascular complications after liver transplantation. *Am. J. Surg.*, 2002, **183** : 595-599.
22. KOBASHIGAWA J.A., KASISKE B.L. Hyperlipidemia in solid organ transplantation. *Transplantation*, 1997, **63** : 331-338.
23. CHARCO R. Dyslipidemia and long-term immunosuppression. *Transplant. Proc.*, 2002, **34** : 124-126.
24. MAC DONALD A.S. Impact of immunosuppressive therapy on hypertension. *Transplantation*, 2000, **70** (11).
25. HENRY M.L. Cyclosporine and tacrolimus : a comparison of efficiency and safety profiles. *Clin. Transplant.*, 1999, **13** : 209-220.
26. MIDTVEDT K., NEUMAYER H.H. Management strategies for post transplant hypertension. *Transplantation*, 2000, **70**.
27. ELLIOT W.J. Traditional drug therapy of hypertension in transplant recipients. *J. Hum. Hypertens.*, 1998, **12** : 845-849.
28. JINDAL R.M., SIDNER R.A., MILGROM M.L. Post-transplant diabetes mellitus ; the role of immunosuppression. *Drug Saf.*, 199, **16** : 242-257.
29. OJO A.O., HELD P.J., PORT F.K. *et al*. Chronic renal failure after transplantation of a nonrenal organ. *N Engl. J. Med*., 2003 Sept. 4, **349** : 931-40.
30. GONWA T.A., MAI M.L., MELTON L.B. *et al*. End-stage renal disease after orthotopic liver transplantation using calcineurin-based immunotherapy. *Transplantation*, 2001 ; **72** : 1934-39.
31. KIZILISIK A.T., GREWAL H.P., SHOKOUH-AMIRI M.H. *et al*. Ten years immunosuppressiwe therapy following orthotopic liver transplantation : impact on health and quality of life. *Transplant. Proc*., 2001, **33** : 3448-3449.
32. NINKOVIC M., LOVE S., BRIAN D.M. *et al*. Lack of effect of intravenous pamidronate on fracture incidence and bone mineral density after orthotopic liver transplantation. *J. Hepatol*., 2002, **37** : 93-100.
33. HAAGSMA E.B., HAGENS V.E., SCHAAPVELD M. *et al*. Increased cancer risk after liver transplantation : a population – based study. *J. Hepatol*., 2001, **34** : 84-91.
34. NORIN S., KIMBY E., ERICZON B.G. *et al*. Posttransplant lymphoma – a single-center experience of 500 liver transplantations. *Med. Oncol*., 2004 ; **21** : 273-84.
35. DE BONA M., PONTON P., ERMANI M. *et al*. The impact of liver disease and medical complications on quality of life and psychological distress before and after liver transplantation. *Journal of Hepatology*, 2000, **33** : 609-615.
36. BRAVATA D.M., OLKIN I., BARNATO A.E. *et al*. Health-related quality of life after liver transplantation : a meta analysis. *Liver Transpl. Surg*., 1999, **5** : 318-331.
37. GEEVERGHESE S.K., BRADLEY A.E., WRIGHT J.K. *et al*. Outcomes analysis in 100 liver transplantation patients. *Am. J. Surg*., 1998, **175** : 348-353.
38. LEVY M.F., JENNINGS L., ABOULJOUD M.S. *et al.* Quality of life improvements at one, two, and five years after liver transplantation. *Transplantation*, 1995, **59** : 515-518.
39. PINSON W.C., FEURER I.D., PAYNE J.L. *et al*. Health-related quality of life after different types of solid organ transplantation. *Ann. Surg*., 2000, **232** : 597-607.
40. COLLIS I., BURROUGHS A., ROLLES K. *et al.* Psychiatric and social outcome of liver transplantation. *British J. Psychiatry*, 1995, **166** : 521-524.
41. HILBRANDS L.B., HOITSMA A.J., KOENE R.A.P. The effect of immunosuppressive drugs on quality of life after renal transplantation. *Transplantation*, 1995, **59** : 1263-1270.