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Adult liver transplantation and steroid-azathioprine withdrawal in cyclosporine (Sandimmun)-based immunosuppression – 5 year results of a prospective study

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Abstract New immunosuppressants are said to be superior to cyclosporine due to their higher incidence of steroid sparing and to the reduced incidence of side-effects. From May 1992 to February 1995, 79 adults underwent primary liver transplantation using cyclosporine A (Sandimmun)-based triple drug immunosuppression. Nine patients who died early after liver transplantation due to reasons unrelated to immunological problems were excluded from this analysis. The long-term outcome of the remaining 70 patients was prospectively studied in relation to steroid and azathioprine withdrawal. They were re-evaluated 6-monthly in relation to liver and kidney function; cholesterolemia, infection, de novo diabetes mellitus and arterial hypertension, malignancy, ophthalmological and osteomuscular diseases. In case of rejection occurring during or after steroid tapering, patients were switched, by protocol, to tacrolimus therapy. Median follow-up was 81 months (range 60–96). Forty-four patients (62.8%) were biopsied 5 years after transplant; 20 patients (28.6%) were biopsied at a median follow-up of 32 months (range 7.8–47). Six patients (8.6%) who refused biopsies more than 1 year after liver transplantation had normal liver values throughout the whole follow-up period. Five-year actual patient and graft survivals were 75% and 65.8%, respectively, for the whole group ($n = 79$) and 85.7% and 74.3% for the studied group ($n = 70$). Steroids could be withdrawn in all but two patients (97.1%) at a median time of 7 months (range 3–42). Steroids were restarted in six patients (8.6%) for extrahepatic reasons. Freedom from steroids was thus observed in 62 patients (88.6%). Seven patients (10%) had rejection after steroid tapering; six were switched to tacrolimus. Two patients (2.9%) needed retransplantation because of acute and chronic rejection whilst still being on full immunosuppression. In total, three patients (4.3%) had histological signs of chronic rejection during follow-up. At 5 years post-transplant, 66.6% and 13.3% of the 60 patients at risk were on cyclosporine and tacrolimus monotherapy, respectively; 93.3% were steroid-free. Mean creatinine and cholesterol levels were 1.56 ± 1.3 mg/dl and 193.5 ± 56.6 mg/dl; incidences of de novo arterial hypertension, insulin dependent diabetes mellitus were 26.6% and 13.3%. Two patients (2.8%) developed post-transplant lymphoproliferative disease, two (2.8%) had skin cancer. Cyclosporine-based immunosuppression allows safe steroid withdrawal in most patients and cyclosporine monotherapy can be achieved in two-thirds without compromising graft and patient survival. Results of new immunosuppressive strategies should be approached

with caution, especially when considering steroid sparing and the incidence of side-effects.

Keywords Liver transplantation · Immunosuppression · Steroid withdrawal · Monotherapy · Side-effects

Introduction

Although results of liver transplantation have markedly improved during the last decade, too many patients die due to infectious, cardiovascular and tumorous complications [2, 26]. Minimal immunosuppression (IS) is therefore warranted [46].

Seventy consecutive adult patients, undergoing liver transplantation using cyclosporine A (Sandimmun; Novartis, Switzerland) based triple drug immunosuppression (IS) and surviving more than 3 months after liver transplantation, were prospectively studied in relation to the feasability of steroid and azathioprine withdrawal and in relation to treatment with cyclosporine monotherapy. This study reports results obtained at 5 years, focusing on "steroid-related" side-effects of IS.

Materials and methods

During the period May 1992 to February 1995, 79 consecutive adults underwent primary liver transplantation, using azathioprine (Imuran; Glaxo-Wellcome, UK), low-dose steroid (Medrol; Upjohn, Sweden) and cyclosporine A (Sandimmun) based triple drug IS.

Nine patients dying early (< 3 months) after liver transplantation in absence of allograft rejection were excluded from this study. Causes of early deaths were perioperative surgical complications (four patients), graft versus host disease related to incompatible allograft transplant (one patient), iatrogenic pulmonary bleeding (one patient), trimethoprim related Lyell syndrome (one patient), early tumor recurrence (one patient) and donor related tuberculosis (one patient). The three latter patients were already steroid-free at moment of death.

The remaining 70 patients, 30 women and 40 men, median age 45 years (range 16.6–68.4) and who survived for more than 3 months were considered in this analysis. Fifty-eight patients were transplanted electively, 12 urgently. Indications for liver transplantation were cholestatic disease (eight patients), parenchymatous disease (51 patients), hepatobiliary tumor (three patients), familial amyloidosis (one patients) and acute liver failure (seven patients).

Child-Pugh classification was A in five patients, B in 21 patients and C in 31 patients.

All but two patients had a piggy-back allograft implantation without use of veno-venous bypass. Median intensive care unit stay was 1.5 days (range 1–24), median hospital stay was 21 days (range 10–100).

All patients received identical intra- and postoperative care. Systemic antimicrobials were administered for 4 days; low risk patients (having elective and non-hemorrhagic transplant procedures) received oxacillin and temocillin whilst high risk patients (having fulminant hepatic failure, previous prolonged hospital and ICU stay, recent history of infection, urgent and/or hemorrhagic procedures) received ceftazidim and vancomycin. Low dose amphotericin B was given intravenously for 10 days. Oral selective bowel decontamination using a mixture of tobramycin, polymixin and amphotericin B was given during the entire hospital stay.

Cytomegalovirus (CMV) prophylaxis using gancyclovir IV (Cymevene; Roche, Switzerland) was used for 3 weeks in all but CMV negative donor-recipient pairs. Oral acyclovir (Zovirax; Glaxo Wellcome) was given for 5 months as herpes simplex prophylaxis. Trimethoprim-sulfamethoxazole (Bactrim; Roche), was given 3 times a week as antiprotozoal prophylaxis until cyclosporine monotherapy was achieved.

The IS protocol consisted of low-dose steroids (360 mg methylprednisolone during the first 10 days), azathioprine (1–2 mg/kg) and cyclosporine (Sandimmun). No patient was on cyclosporine microemulsion (Neoral® Novartis, Switzerland). Specific cyclosporine whole-blood through levels of 100–150 ng/ml (determined by monoclonal fluorescence assay) were aimed for. Corticosensitive rejection was treated with five boluses of 200 mg methyprednisolone. Corticoresistant rejection, defined as non-response to 1 g methylprednisolone, was treated with a 10-day IV course of OKT3 (muromonab monoclonal antibodies; Cilag-Jansen, USA).

Steroid reduction was started from week 6 in order to obtain freedom from steroids within the first year. Steroid withdrawal, which was done independently of previous antirejection treatment, was followed by azathioprine withdrawal in order to achieve cyclosporine monotherapy.

Steroid tapering was slowed down in 49 patients (70%) for the following reasons: hepatitis C allograft reinfection (28 patients), autoimmune liver disease (eight patients), renal insufficiency at moment of transplantation (creatinine clearance less than 20 ml/min) (six patients), inflammatory bowel disease (two patients), 100% crossmatch positivity (two patients) and retransplantation (ten patients).

Patients presenting with rejection after steroid withdrawal or taper were switched, by protocol, to tacrolimus (Tac) (Prograft; Fujisawa, Japan).

Bilirubin, ALT, GGT, creatinine and cholesterol levels (expressed as mean ± SD), incidence of de novo bacterial, viral and fungal infections, arterial hypertension, insulin dependent diabetes mellitus, malignancy, osseous related (severe osteomuscular pain, osteonecrosis and/or fractures) and ophthalmological (cataract) complications were recorded every 6 months. Liver test values up to 1.5 times normal were considered normal. Hypercholesterolemia was defined as fasting serum cholesterol level greater than 220 mg/dl. Following WHO guidelines, arterial hypertension was defined as systolic and diastolic pressures above 140 and 100 mmHg.

Diagnosis of bacterial and fungal infections was based on the presence of positive cultures; viral infection was diagnosed based on tissue culture positivity, seroconversion and/or 4-fold elevation of IgG titers.

Protocol liver allograft biopsy was carried out at day 7 and afterwards when indicated. Five-year liver biopsies, proposed to all surviving patients, were done in 44 patients (62.8%). Twenty patients (28.6%) had biopsies at a median follow-up of 32 months (range 7.8–47) and six patients (8.6%) who refused protocol biopsies after the first year post-transplant had normal liver test values throughout the whole study period.

Diagnosis of rejection was based on the combination of clinical, histological and biochemical changes. Portal tract infiltration, bile

Table 1 Infuence of previous rejection and of OKT3 treatment on timing of steroid withdrawal and obtention of cyclosporine monotherapy

Rejection	Delay between transplantation and	
	Steroid withdrawal (months)	CyA monotherapy (months)
No treatment	6.9 ± 3.1	17.6 ± 14
OKT3 therapy no	7.3 ± 2.7	20.5 ± 14.5
OKT3 therapy yes	9.3 ± 6.2	18.4 ± 11.6 NS

duct changes and endothelitis were scored from 0 to 3. Chronic rejection (ductopenia) was defined in the presence of more than 50% bile duct loss on a representative biopsy [6].

Follow-up was complete for all patients with a minimum of 60 months from date of liver transplantation. Median follow-up was 82 months (range 7.8–96).

Results are reported up to 5 years post-transplant.

Results

Five-year actual patient and graft survivals for the whole patient group ($n = 79$) were 75.9% and 65.8% and 85.7% and 74.3% for the studied patient group ($n = 70$).

The causes of death during the 60-month follow-up period were cerebral bleeding (13 months), chronic rejection (13 months), recurrent allograft HCV infection (8, 31, 37, 57 months) recurrent cholangiocarcinoma (37 months), cardiac failure (49 months), de novo allograft HBV infection (54 months), and recurrent autoimmune hepatitis (57 months). One patient died at 16 months due to chronic rejection. All IS had been stopped following the diagnosis of post-transplant lymphoproliferative allograft disease (PTLD). Unfortunately, this patient could not be retransplanted in time; autopsy confirmed complete regression of the PTLD.

Seventeen patients (24.3%) did not have any rejection episodes. Twenty-six (37.1%) and 27 patients (38.6%) developed corticosensitive and corticoresistant rejections. Two patients (2.9%) were retransplanted for uncontrollable acute (at day 25) and chronic (at day 70) rejection, whilst still being under full dose triple drug IS.

Steroids were withdrawn in 68 patients (97.1%) at a median time of 7 months (range 3–42). Two (2.9%) patients remained on full dose steroids because of severe previous rejection necessitating combined kidney and liver retransplantation (one patient) and because of preexisting renal insufficiency (creatinine clearance < 20 ml/min) precluding use of Cyclosporine (one patient). Steroids had to be reintroduced six times (8.6%) because of HCV-related arthralgia and vasculitis (two patients); recurrent autoimmune hepatitis and Crohn's disease (one patient), Crohn's disease (one patient), late rejection and psoriasis (one patient) and pemphigus (one patient). Freedom from steroids was thus observed in 62 patients (88.6%).

Seven patients (10%) had rejection during steroid taper or just after steroid withdrawal.

Previous therapeutic use of OKT3 did not influence significantly timing of steroid withdrawal and incidence of cyclosporine monotherapy (Table 1). The evolution of the incidence of steroid withdrawal and of cyclosporine monotherapy is shown in Table 2.

Sixteen patients (22.9%) were permanently (13 patients) or temporarily (three patients) switched to Tac for rejection related to: steroid withdrawal (six patients); erroneous diagnosis of rejection (five patients) [intrahepatic biliary strictures (three patients) and recurrent hepatitis (two patients)]; cyclosporine-related neurotoxicity (two patients) and gingival hyperplasia (one patient); rejection due to non-compliance (one patient) and finally IS withdrawal necessary to overcome severe biliary sepsis (one patient).

Eight (11.4%) of 70 patients were therefore switched to Tac for immunological reasons.

Despite lowering of cyclosporine doses and low cyclosporine blood levels, creatinine levels rose slowly but progressively over time (Fig. 1). Two patients required hemodialysis and one had a living related kidney transplantation 4 years post-transplant (Table 3).

Table 2 Flow diagram of steroid withdrawal and cyclosporine monotherapy during 60 months of follow-up

Follow-up (months)	6	12	24	36	48	60
Patients at risk (n)	70	69	66	65	63	60
Steroid withdrawal (%)	44.3	75.7	93.9	87.9	90.3	91.7
Cyclosporine monotherapy (%)	7.1	40	62.1	69.7	74.2	66.6
Tac monotherapy (%)	0	4.3	6.1	7.6	11.3	13.3

Table 3 Evolution of immunosuppression doses per kg body weight (mean ± SD) during 60 months of follow-up

Follow-up (months)	6	12	24	36	48	60
Patients at risk (n)	70	69	66	65	63	60
Cyclosporine (mg/kg)	4.1 ± 1.8	3.3 ± 1.7	2.5 ± 0.1	2.3 ± 1	2 ± 1.1	1.6 ± 1.1
Steroids (mg/kg)	0 ± 0.1	0 ± 0.07	/	0 ± 0.1	0 ± 0.05	0 ± 0.05
Azathioprine (mg/kg)	0 ± 0.6	0 ± 0.4	0 ± 0.3	0 ± 0.3	0 ± 0.2	0 ± 0.2
Tac (mg/kg)	0 ± 0.1	0.1 ± 0.1	0.1 ± 0.07	0.1 ± 0.13	0.08 ± 0.5	0.66 ± 0.5

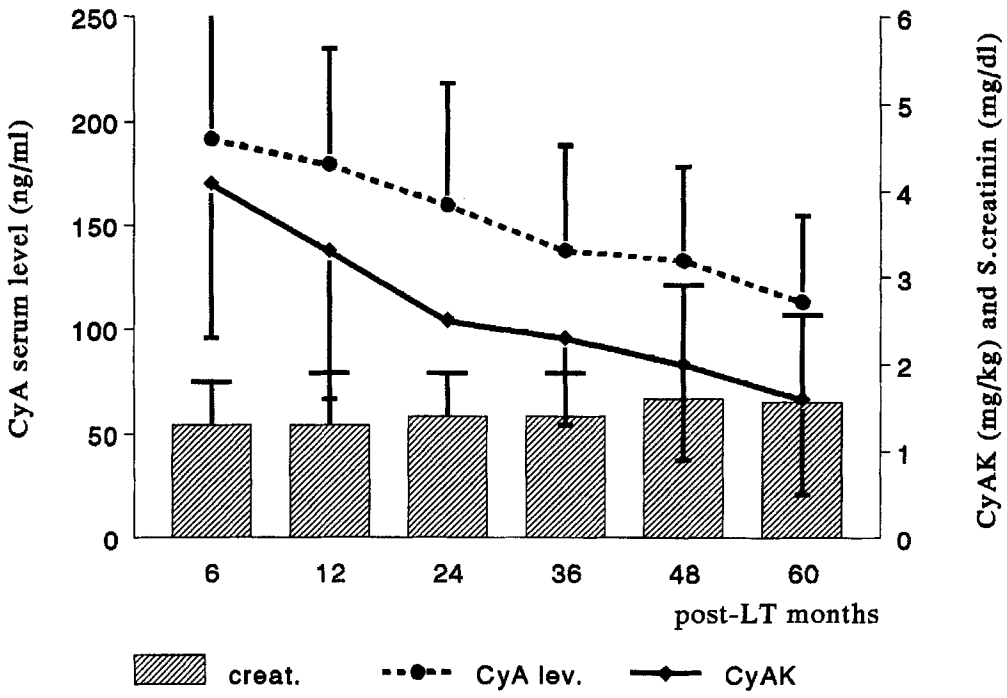

Fig. 1 Relation between creatininemia, cyclosporin levels and doses during the 60 months of follow-up

Table 4 Incidence of side-effects of immunosuppression during 60 months of follow-up

Follow-up (months)	6	12	24	36	48	60
Patients at risk (*n*)	70	69	66	65	63	60
Creatinine (mg/dl)[a]	1.3 ± 0.5	1.3 ± 0.6	1.4 ± 0.5	1.4 ± 0.5	1.6 ± 1.3	1.56 ± 1[b]
Cholesterol (mg/dl)[a]	211 ± 65	195 ± 48.3	187 ± 51.5	194 ± 48	193 ± 51.5	201.4 ± 56.6
De novo arterial hypertension (%)	37.1	27.1	25.8	36.4	30	26.6[c]
De novo insulino-dependent diabetes (%)	27.5	10	6	10.6	9.7	13.3
Malignancy (%)	1.4[e]	1.4[d]	–	–	1.6[e]	1.7[d]
Osseous (fracture) (%)	10 (7)	12.8 (7)	5.9	5.9	9.7 (1.6)	14.5 (0)
Cataract surgery (%)	2.8	2.8	1.5	1.5	2.1	0
De novo infection						
Bacterial	45.7	12.8	3	9.1	4. 7	1.6
Viral	32.8	8.6	3	4.5	–	1.6
Fungal	18.6	7.1	1.5	–	–	–

[a] Mean ± SD
[b] Two patients on chronic hemodialysis; one patient had living related renal transplantation
[c] Five (8.3%) of 60 patients were on double drug therapy
[d,e] Cumulative incidence of malignancy 5.8% (4/70 patients): skin cancer[d] (two patients) and PTLD[e] (two patients)

At 60 months, 20 (50%) of 40 cyclosporine monotherapy and six (75%) of eight Tac monotherapy patients had subtherapeutic levels (< 100 ng/ml or < 6 ng/ml, respectively).

Incidences of different side-effects of IS during follow-up are given in Table 4.

Two patients (2.9%) had skin cancer, one spinocellular and one basocellular, the latter in the context of severe pre-transplant psoriasis. Two patients (2.9%) had PTLD; both tumors disappeared completely after IS withdrawal. The first patient developed PTLD in the allograft. He had never presented with rejection and he only had one early episode of CMV infection; he was steroid free at 3 months post-transplant. IS withdrawal cured the PTLD but at the price of chronic rejection. Unfortunately he could not be retransplanted in time. The second patient developed peritoneal PTLD 42 months post-transplant; he was also cured after stopping IS. All liver tests remained normal but he died of a myocardial infarction 7 months later.

At the end of the 60-month follow-up period, 23 of 60 patients (41.7%) had abnormal GGT values and 17 patients (28.3%) had abnormal ALT values. Both values were raised in 12 patients (20%). The reasons for abnormal liver biochemistry were non-specific hepatitis (ten patients), recurrent HCV allograft reinfection (five pa-

Table 5 Results of liver biopsies carried out more than 1 year after transplantation in 63 long-term (> 3 months) survivors[a]

≥ 60 months post-LT $n = 44$	13–47 months post-LT (median 32) $n = 19$
Recurrent allograft disease 15	Recurrent disease 8
HCV-hepatitis 10	HCV-hepatitis 7
Cirrhosis 1	Cirrhosis 1
Autoimmune hepatitis 2	
Primary biliary cirrhosis 1	
Paromyxovirus hepatitis 1	
Aspecific chronic hepatitis 11	Aspecific chronic hepatitis 3
Steatosis (and hepatitis) 5 (3)	
Normal 9 (20.4%)	Normal 6 (31%)
De novo B hepatitis 1	
Ischaemic biliary tract lesions with cholangitis 1	
Toxic isoniazide hepatitis 1	
Chronic rejection 1	*Chronic rejection 2*[b]

[a] Six patients having normal liver tests during whole follow-up refused biopsy more than 1 year after transplant and one patient died 7.8 months post-transplant due to cholestatic HCV-hepatitis

[b] One patient retransplanted under triple drug Tac-based IS; the second allograft was also lost due to chronic rejection

tients), ischemic biliary tract lesions (three patients), de novo HBV infection (one patient), recurrent autoimmune hepatitis (two patients), toxic isoniazide related hepatitis (one patient) and steatosis (one patient).

Findings of long-term liver biopsies in 63 patients are listed in Table 5. Three patients (4.3%) developed chronic rejection. One patient, transplanted because of amoxycillin-related acute liver failure, was retransplanted at day 70 because of chronic rejection; the second graft was also lost due to chronic rejection despite reinforced triple-drug Tac-based IS.

One young female with primary sclerosing cholangitis and severe Crohn's disease developed chronic rejection in the context of poor compliance towards her IS therapy as well as to her colitis treatment. Another female who was transplanted for primary biliary cirrhosis developed severe chronic rejection 5 years post-LT, due to subtherapeutic IS related to a prolonged period of untreated diarrhea.

Discussion

The introduction of cyclosporine based IS in the 1980s was the main factor leading to the exponential growth of extrarenal transplantation. During the past few years the field of solid organ transplantation has been overwhelmed by the development of many new drugs leading to numerous studies [14, 23, 32]. Many of these conclude the superiority of one immunosuppressant over another based on the rate of STWD and on the reduction of steroid-related side-effects [10, 14, 32, 38, 54]. Little attention has, however, been given to the possibility of and the results from STWD in adult [3, 12, 13, 30, 36, 41, 49, 52, 53] and paediatric [1, 9, 28, 30, 31, 50] liver transplantation during the cyclosporine era. This was mainly due to the fear of development of acute and chronic rejection, as documented previously in long-term follow-up in renal transplantation [20, 35, 42, 45, 51].

Eleven studies [3, 13, 14, 30, 36, 38, 41, 47, 48, 52, 53], only four of which were prospective and randomized [3, 30, 48, 53], looked more carefully at the possibility of STWD in adult LT (Table 6). In these studies, induction IS consisted half of quadruple therapy using monoclonal or polyclonal antilymphocytic antibodies and STWD was frequently undertaken more than 1 year after transplant, usually when stable graft function was obtained. Although STWD could be obtained in 68–100% of patients, cyclosporine monotherapy was reached in a majority of patients in only three studies [13, 47, 52]. The incidence of acute and chronic rejection varied widely from 4 to 55.1% and from 0 to 6.9% of patients.

Significant advantages of STWD in relation to arterial hypertension, cholesterolemia-lipidemia, diabetes mellitus and/or incidence of osteomuscular disease have been reported in liver [3, 13, 41, 44, 47, 48, 49] and renal transplantation [15, 21, 42]. Our study confirms (a) that steroid and azathioprine withdrawal is possible in the vast majority of adult liver transplants (88.6%) performed under cyclosporine (Sandimmun)-based triple drug IS; (b) that the incidence of chronic rejection is low (4.3%); (c) that infection is not a major problem during late follow-up and (d) that cyclosporine monotherapy (in some cases every at subtherapeutic levels) can be achieved in two-thirds of the 5-year survivors without compromising graft survival. The finding that timing and incidence of STWD and cyclosporine monotherapy was similar in patients with or without previous corticoresponsive or corticoresistant rejection suggests that the real incidence of rejection should be examined more carefully by combining clinical, biochemical and histological data [3, 6, 53]. The lack of close correlation between these parameters may explain the wide range in the incidence of rejection between different centers [3, 34, 37, 53, 55]. The high incidence of acute rejection in this study, related moreover to the fear for graft loss in the presence of rapid tapering of IS. It is probable that a significant number of patients reported in this, as well as in other studies, did not require rejection treatment at all. This observation weakens the conclusions of many multicenter IS studies.

Reduction of side-effects may be one of the factors explaining improved survival after cyclosporine monotherapy in solid organ transplantation [35]. The slow, but progressive, rise of creatinine and the development of end-stage renal failure despite repeated reduction of

Table 6 Steroid withdrawal and adult liver transplantation: literature review. *MMF* Mycophenolate mofetil, *Tac* tacrolimus, *CyA* cyclosporine A, *Ster* steroids, *Aza* azathioprine, *AT(L)G* anti-thymocytes (lymphocyte) globulins

Year	Author	Reference	Center	Induction IS	No. patients		Steroid withdrawal time (months)	Success (%)	Acute rejection (%)	Chronic rejection (%)	Follow-up (months)	Advantages	Particularities
1993	Padbury	36	Birmingham, UK	CsA-Aza-Ster	197		≥ 3 (1–32)	85 → 71[c]	4.5	3.9	28 median (5–109)	Arterial hypertension Infection Diabetes	CyA monotherapy (47.2%)
				CsA-Ster									
1995	Punch	41	Ann Arbor	CsA-Aza-Ster-ATG/MALG	51		≥ 12 stable graft	88	12	–	13.8 median (4–36)	Arterial hypertension[b], cholesterolemia[b]	
1995	McDiarmid[a]	30	Los Angeles	CsA-Aza-Ster	64	33 (24 ad) 31 (17 ad)	≥ 12 /	94 /	6.5 6	0 0	23 mean	Cholesterolemia	
1996	Tchervenkov	52	Montreal	CsA-Ster-ATG-Aza	42		≥ 12	93	9	–	3–12	Cholesterolemia,[b] diabetes,[b] arterial hypertension[b]	CyA monotherapy (93%)
1996	Fraser	12	London, UK	CsA-Aza-Ster. ± ATG	114		6.7 ± 3.9	84.2	8.3	3	27 ± 18.5	Diabetes	CyA monotherapy (29.2%)
1997	Stegall	47	Denver	CsA-Ster	28		> 24	75	14.2	–		Arterial hypertension, diabetes, cholesterolemia[b]	CyA monotherapy (75%)
1997	Stegall[a]	48	Denver	CsA-Ster-MMF (Neoral)	71	36	0.5	100[d]	46	–		Cholesterolemia[b], arterial hypertension[b], diabetes[b]	CyA–Tac monotherapy at 6 months (21.4%)
				Tac-Ster-MMF		35	0.5	88.2	42.3		> 6		
1997	Pichlmayr	38	European Multicenter	Tac-Ster	529	264	36	80.3	45. 4	2	36		
				CyA-Aza-Ster ± ATG		265		68.1	55.1	6.9			
1998	Gomez	13	Madrid	CsA-Aza-Ster	86		> 12 stable graft (36 ± 18)	100	0	0	23 mean (12–58)	Arterial hypertension[b], body weight[b], cholesterolemia[b], bone disease[b], diabetes	CyA monotherapy (83.5%)
1998	Belli[a]	3	Milan	CsA-Aza-Ster-ATG	104	54	> 3 (4–5)	98.5[e]	4	0	41 mean (4–68)	Arterial hypertension[b], diabetes[b]	
						50	/	/	8	3			
1998	Tisone[a]	53	Rome	CsA-Aza-Ster	45	22	3	100	9.1	0	14 median (6–24)	Diabetes[b],	
				CsA-Aza (Neoral)		23	/	/	8.7	0		cholesterolemia[b]	
1999	Lerut		Brussels-UCL	CsA-Aza-Ster (Sandimmun)	70		7 (3–42)	97.1 → 88.6[c]	10	4.3	≥ 60 (7.8–96)	Arterial hypertension, diabetes, cholesterolemia, bone disease	CyA monotherapy at 60 months (66.6%)

[a] Randomized prospective studies
[b] Statistically significant improvement
[c] Steroid therapy restarted because of reasons other than rejection
[d] 12.5% of patients switched to Tac because of recurrent rejection
[e] Long-term therapy restarted because of intractable pruritus and severe cholestasis in one patient

cyclosporine (even to subtherapeutic levels) is of major concern. Time of exposure and total dose of nephrotoxic IS have been shown to be determining factors in renal impairment [11]. More effort must therefore be made to avoid cyclosporine nephrotoxicity during the critical first post-transplant months [4, 11, 17, 39, 44] and subtherapeutic levels of nephrotoxic IS drugs should be aimed for as soon as possible. Nephrotoxic drug discontinuation can be safe if doses of other non-nephrotoxic drugs are altered [4, 17].

Retrospective studies have shown, that hypercholesterolemia [5] and post-transplant diabetes mellitus [33] are similar in cyclosporine- and Tac-based monotherapy IS regimens. This may explain the lower incidences of arterial hypertension, insulin dependent diabetes mellitus and hypercholesterolemia in this study compared to recent publications [5, 16]. These observations confirm that it is not the main immunosuppressant but the associated steroid therapy which is the culprit for the "(dis)advantages" of one or the other drug [6]. Several IS studies therefore conclude that a new drug is superior on unjustified grounds [16, 33, 38]. It is mandatory to have better and more objective information in relation to the real incidence of rejection and of side-effects of IS by conducting studies in centers that have extensive experience in the management of transplanted patients. Diagnosis of rejection must be based on internationally accepted scoring systems [6] in order to establish guidelines for modifications in IS [8, 34, 46, 55].

The lowest possible IS regimen must be the strategy for the future [7, 9, 37, 46]. This will reduce side-effects to a minimum that will in turn improve quality of life and also reduce the costs of transplantation [19]. This attitude is especially justified when transplanting the immunologically privileged liver graft. Even severe histological rejection can reverse spontaneously [34] and, in contrast with renal transplantation, single episodes of acute rejection do not impair long-term graft survival [3, 8, 55]. IS can be stopped temporarily for life-threatening infections and tumors [27]; some patients can be weaned completely [7, 29, 46].

The advantages and disadvantages of a completely steroid-free regimen versus steroid withdrawal need to be elucidated in prospective, double blind, placebo controlled randomized trials [3, 42, 48, 51, 53]. Reduction, withdrawal or even avoidance of steroids from the day of transplantation should be aimed for, as many side-effects may become irreversible once steroid treatment has begun [11, 15, 16, 51].

Results of new immunosuppressive drugs and strategies should be approached with caution in relation to incidence of steroid use or sparing and the incidence of side effects. The favorable results obtained in LT in relation to steroid use will affect future attitudes in renal, pancreas and heart transplantation [22, 24, 25, 40, 42, 43]. More careful interpretation of the results of the multitude of ongoing, often industry driven, immunosuppressive studies in solid organ transplantation is mandatory in order to progress.

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