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WEANING OF IMMUNOSUPPRESSION IN LONG-TERM LIVER TRANSPLANT RECIPIENTS,[1,2]

Hector C. Ramos[3], **Jorge Reyes**, **Kareem Abu-Elmagd**, **Adriana Zeevi**, **Nancy Reinsmoen**, **Andreas Tzakis**, **Anthony J. Demetris**, **John J. Fung**, **Bridget Flynn**, **John McMichael**, **Fred Ebert**, and **Thomas E. Starzl**
The Transplantation Institute, University of Pittsburgh Medical Center, and the Veterans Administration Medical Center, Pittsburgh, Pennsylvania

Abstract

Seventy-two long-surviving liver transplant recipients were evaluated prospectively, including a baseline allograft biopsy for weaning off of immunosuppression. Thirteen were removed from candidacy because of chronic rejection (n=4), hepatitis (n=2), patient anxiety (n=5), or lack of cooperation by the local physician (n=2). The other 59, aged 12–68 years, had stepwise drug weaning with weekly or biweekly monitoring of liver function tests. Their original diagnoses were PBC (n=9), HCC (n=1), Wilson's disease (n=4), hepatitides (n=15), Laennec's cirrhosis (n=1), biliary atresia (n=16), cystic fibrosis (n=1), hemochromatosis (n=1), hepatic trauma (n=1), alpha-1-antitrypsin deficiency (n=9), and secondary biliary cirrhosis (n=1). Most of the patients had complications of long-term immunosuppression, of which the most significant were renal dysfunction (n=8), squamous cell carcinoma (n=2) or verruca vulgaris of skin (n=9), osteoporosis and/or arthritis (n=12), obesity (n=3), hypertension (n=11), and opportunistic infections (n=2). When azathioprine was a third drug, it was stopped first. Otherwise, weaning began with prednisone, using the results of corticotropin stimulation testing as a guide. If adrenal insufficiency was diagnosed, patients reduced to <5 mg/day prednisone were considered off of steroids. The baseline agents (azathioprine, cyclosporine, or FK506) were then gradually reduced in monthly decrements. Complete weaning was accomplished in 16 patients (27.1%) with 3–19 months drug-free follow-up, is progressing in 28 (47.4%), and failed in 15 (25.4%) without graft losses or demonstrable loss of graft function from the rejections. This and our previous experience with self-weaned and other patients off of immunosuppression indicate that a significant percentage of appropriately selected long-surviving liver recipients can unknowingly achieve drug-free graft acceptance. Such attempts should not be contemplated until 5–10 years posttransplantation and then only with careful case selection, close monitoring, and prompt reinstitution of immunosuppression when necessary.

Lifetime immunosuppression has been a presumed necessity after clinical whole-organ transplantation. However, we have suggested elsewhere that liver allograft acceptance without a need for maintenance immunosuppression may have been accidentally achieved more often than realized (1). The recently proposed concept that donor leukocyte migration and long-term microchimerism is the basis of allograft acceptance (2) would account for the

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[3]Address requests for reprints to Hector C. Ramos, M.D., Division of Transplantation, University of New Mexico Health Sciences Center, 2211 Lomas Blvd, NE, Albuquerque, NM 87131.

slow evolution of the self-sustaining drug-free tolerance that has been most frequently seen in, but not confined to, liver recipients (3).

The possibility of drug weaning had previously been demonstrated by 6 noncompliant liver recipients who were found in April 1992 to have successfully discontinued all medications from 5 to 13 years previously (1), and by 5 more with EBV-associated B cell lymphomas whose drugs had been stopped 6 months to 8 years posttransplantation with subsequent drug-free survival for 0.5 to 2.8 years (4). The present prospective weaning study did not include these 11 earlier recipients, all of whom continue to be well with 1½ to 2½ more years of follow-up.

We describe here a prospective trial of drug weaning of 59 more long-surviving liver recipients, all of whom had complications of chronic immunosuppression. All patients reported with complete drug discontinuance have been observed subsequently for 6.5 to 22.5 months.

MATERIALS AND METHODS

Case material

Between June 1992 and March 1994, 72 patients were evaluated for the weaning protocol. Candidacy criteria were: (1) ≥5 yr post-transplantation; (2) ≥ yr without episode of rejection; (3) history of medical compliance; (4) evidence of complications related to chronic immunosuppressive therapy; (5) primary physician cooperation; and (6) baseline liver biopsy showing no evidence of rejection or severe hepatic disease. Thirteen of the 72 patients were withdrawn from the candidacy list because of biopsy evidence of acute or chronic rejection (n=4), severe hepatitis on biopsy (n=2), patient anxiety (n=5), and refusal of cooperation by primary physician (n=2). The remaining 59 included 20 who were 12–20 years old when weaning was started, and 39 who were 21–68.

Baseline immunosuppression

The drugs regimens from which weaning occurred were: azathioprine and prednisone (AZA/PRED) (n=10), cyclosporine and prednisone (CsA/PRED) (n=19), cyclosporine and azathioprine (CsA/AZA) (n=3), cyclosporine, azathioprine, and prednisone (CsA/AZA/PRED) (n=12), cyclosporine alone (CsA) (n=9) and tacrolimus (FK506, Prograf) (n=6). The 6 patients on tacrolimus had been converted from other regimens earlier in their course.

Weaning protocol

If AZA was part of triple therapy, it was weaned before beginning prednisone reduction, but if it was the principal immunosuppressant it was weaned in the same way as the other baseline drugs (see below). Patients still receiving prednisone were begun with a 25–50% steroid reduction. In the event of hepatoceliular enzyme elevation, no further changes were made until the enzymes stabilized. Further decrements in prednisone were at one-month intervals. Corticotropin stimulation testing was used to detect adrenal cortical insufficiency before complete steroid withdrawal. Corticotropin (.25 mg) was administered intravenously after obtaining a baseline serum cortisol level. Serum cortisol was then measured at 30 and 60 min post–corticotropin administration (5). Patients with normal adrenocortical function responded to stimulation with >7 μg/dl increase in serum cortisol.

Reduction of the baseline immunosuppressive agents, CsA, AZA, and tacrolimus (FK506, Prograf) also were considered every month. CsA was reduced by 10–25%/month until blood levels were <50 ng/ml for 3 months and then by 50%/month until cessation. A similar protocol was used for FK506.

Baseline enzyme measurements of AST, ALT, GGTP, and serum bilirubin were performed weekly or biweekly between the monthly decision points, as well as CsA and FK506 trough levels. Enzyme elevations or patient symptoms triggered an increased frequency of liver function tests, and a judgment about restoration of immunosuppression. In reaching a decision, the preweaning biopsy was invaluable for comparison with subsequent ones.

Chimerism studies

Microchimerism studies had been performed previously on 13 of the 59 patients, all of whom had donor cells or DNA demonstrated in peripheral tissues, or blood by the detection of Y chromosome in female patient recipients of male donor organs, or by the detection of donor specific HLA alleles—using cytostaining and polymerase chain reaction (PCR) techniques (1,2). Because chimerism was invariably demonstrable in all of our long-surviving liver and kidney allograft recipients, it was assumed to be present in the rest of the cases of the present study and these tests were not performed.

In-vitro testing: homozygous typing cells (HTC)

Twenty-six patients were studied. To assess the development of donor-specific hypo reactivity, their peripheral blood mononuclear cells (PBMC) were tested in standard mixed lymphocyte reaction (MLR) against a panel of homozygous typing ceils (HTC) as previously described (6). These stimulator cells were selected based on their homozygosity for HLA-DR and in each assay HTCs for 7 different Dw specificities were included, with 2–3 HTCs per specificity. Each responder was tested with HTCs that identified “self” specificities, HTCs that defined the donor DR type, and unrelated control third party stimulators. The results were expressed as double normalized values (DNVs). Immune responsiveness was evaluated through mitogen induced proliferation. Isolated mononuclear cells from patients heparinized blood were cultured. Proliferation (i.e., responsiveness) was assessed by ^{3}H-thymidine uptake after induction with phytohemagglutinin (PHA) and concanavalin A (Con A).

RESULTS

Outcome of weaning

Failure of Weaning. After a follow-up of 6.5 to 22.5 months (mean 15 months) 15 (25.1%) of the 59 patients have had a diagnosis of rejection (Table 1). Three of the 15 were treated without pathologic documentation of rejection and were subsequently placed back on the weaning protocol. There were no graft losses, or examples of jaundice. All liver functions eventually returned to their preweaning values. The enzyme data and summarized in Figure 1.

Rejection in the 12 biopsy-confirmed cases (AJD) was diagnosed by the presence of portal triad cellular infiltrates causing duct damage, duct loss, or central venulitis. Two patients had histologic classification of moderate-to-severe rejection, and the 2 were converted to FK506. The other 10 rejections were classified as minimal-to-mild. When rejection was diagnosed, it was treated with 1 g methyl prednisolone and a 6-day prednisone cycle, starting at 200 mg on the first day and ending at 10 mg/day. Two patients were converted from CsA to FK506. One of these patients, who also required additional pulse steroid therapy, developed herpes keratitis that responded to acyclovir therapy and reduction of immunosuppression. This was the only serious complication in the trial.

Weaning complete or in progress

Sixteen patients (27.1%) are off medications, including 2 kept on <5mg of prednisone due to an unresponsive corticotropin stimulation test. The other 28 (47.4%) are still at various phases of weaning.

Twenty patients, including some fully weaned and still being weaned, had enzyme elevations that spontaneously returned to normal despite further weaning or drug discontinuance (Fig. 2). The enzyme patterns were similar to those in the weaning failure group (compare with Figure 1). In those cases in which biopsies were obtained, the histopathologic findings were nonspecific, including the lobular reactivity or inflammation that is not diagnostic of rejection (7) (Table 2).

Effect on preweaning complications

The most consistent improvement was the involution of verrucous warts. One patient with squamous cell carcinoma of the skin had dramatic improvement with virtual disappearance of lesions 6 months after completion of weaning. Preexisting hypertension and renal dysfunction were not affected (Table 3).

Outcome versus prior immunosuppression

There was a high rate of weaning failure in patients previously treated with triple-or double-drug cyclosporine-based immunosuppression. Good results were obtained if prior treatment was with cyclosporine or with azathioprine/prednisone (Table 4).

Proven chimerism versus outcome

Seven of the 13 patients proved in April–June 1992 to have donor leukocyte chimerism (1) have since been successfully weaned. Two more are still in the process, and 5 were returned to immunosuppression either because of biopsy evidence of rejection (n=4) or unconfirmed suspicion of this diagnosis (n=1).

Homozygous typing cells assay

Results from samples drawn before or close to the onset of weaning were equivocal in 10 of the 26 patients due to low reactivity to all panels or inadequate sampling, making the test impossible to interpret. Of the other 16.8 were reactive to the whole panel. Five have had episodes of rejection and 3 are still weaning (Table 5).

Eight patients were hyporeactive for donor-specific DR antigen only. Five of this group are off medications, 1 is still being weaned, and 2 failed weaning (Table 5).

DISCUSSION

The rationale for this trial was based in part on the previous observation in early 1992 that 15% of our liver recipients followed >10 years had discontinued all medications 5 to 13 years previously without developing rejection (1). With 2½ more years of follow-up, these 6 recipients, who for the most part had reached a drug-free status by noncompliance, are still well with 2½ more years follow-up. A further collection of 5 children whose physician-directed drug discontinuance .5 to 8 years posttransplantation was prompted by the development of Epstein-Barr–associated B cell lymphomas (4) continue to be stable and now have been drug-free for from 1 or to 3.3 years.

The prospective weaning trial herein reported has confirmed our suspicion that many long-term survivors after liver transplantation no longer need chronic immunosuppression at the prescribed levels, if at all. One-fourth of the patients entered have been able to discontinue

immunosuppression altogether, half are still weaning without complications, and only a quarter have failed the effort. No hepatic grafts have been lost and none has suffered measurable damage. The only significant complication was in a patient who developed readily treated herpes keratitis. In 2 examples of histopathologically severe rejection, a safety net was provided by the “rescue” capabilities of FK506 (8) to which the patients were converted.

The need for close and continuance medical surveillance was evident. All of the rejections were signaled without the occurrence of jaundice by rises in the transaminase levels and in the canalicular tests of which the GGTP is the most specific. Confirmatory allograft biopsies were of the utmost importance for management decisions because enzyme rises during weaning were seen with equal frequency in allografts with and without evidence of rejection. There was no clear explanation for the transient enzyme increases in patients whose weaning was not interrupted. One possibility was that there was an unapparent and self-resolving rejection. Another might have been the loss during drug withdrawal of the hepatotrophic effects of either cyclosporine (9) or FK506 (10). Two of these nonrejecting patients have had waxing and waning of the enzyme activity during further weaning or drug stoppage.

Although it is too soon to be confident about the safety of the weaned patients, the demonstration of allograft stability in the previously reported drug-free patients for as long as 15 years is reassuring. In the presently reported prospective study, the peak risk appeared to have been passed by the sixth month. Early dividends of discontinuance of immunosuppression have already been seen, most frequently the involution of benign as well as malignant skin lesions. Disappointingly, there has been no improvement in preexisting arterial hypertension or renal dysfunction.

The subgroup of 13 patients with previously documented chimerism was of special interest. We have emphasized frequently our belief that this chimerism is a cardinal requirement for allograft acceptance and for the potential eventual evolution of donor specific nonreactivity (tolerance) but that it is not synonymous with either outcome. The proposition as originally stated was that “Clinical success—tolerance or graft acceptance—means that a characteristic lymphoid and dendritic cell chimerism has been introduced, which may be stable either without further treatment or only when continued immunosuppression is provided; an unstable graft and its migrated cells may either be rejected or cause GVHD” (2). The heterogeneity of results from weaning in these 13 cases conformed entirely with this central hypothesis. Although 9 of the 13 liver recipients have been able to stop drugs (n=7) or are successfully weaning (n=2), the onset of rejection required resumption of immunosuppression in the other 4.

As discussed in detail elsewhere (11), acceptance of whole-organ allografts and the achievement of a drug-free state are in fact mirror image events to those occurring after successful bone marrow transplantation in cytoablated recipients. The fundamental difference is that the trace leukocyte population in the David/Goliath cell relationship following whole-organ transplantation is donor rather than recipient, with the obvious implication that the principal risk is rejection rather than GVHD. Using this two-way paradigm of transplantation immunology, it is easy to understand the lengthy periods of immunosuppressive coverage that are usually necessary before a drug-free state can evolve. When bone marrow transplantation is from MHC-matched donors, continuous immunosuppression is frequently required for a year or more, and when there are 1 to 3 HLA allele mismatches, a period of 5 years or longer is needed before drugs can be stopped.

The liver transplant recipient has delineated an even more protracted time frame for solid-organ recipients of mismatched whole-cadaver organs (12). The risk in liver recipients of weaning attempts too early, too abruptly, or without frequent testing of allograft function have been described by Sanborn et al. (13) in a series of patients weaned from a cyclosporine-based triple-drug therapy. Moderate-to-severe rejection was frequently encountered in this series of 12 cases, leading to secondary complications after renewal of high-dose immunosuppression and eventually 2 deaths. The difficulty of weaning from cyclosporine when it was part of a triple-drug regimen also was noted in our experience.

Although this study was concerned only with liver allografts, we believe that the same trends can be found with other whole organs if these are systematically looked for. Five of our long-term recipients of living-related kidneys (not twins) have been off of immunosuppression for 1, 1.7, 14, 28, and 29 years (3). However, the lower density of chimerism in kidney and heart recipients undoubtedly makes weaning more hazardous than in the recipient of the inherently tolerant liver, and consequently this has been attempted only when there are immunosuppression-associated life-threatening complications (14).

The inability to accurately predict which patients can be successfully weaned means that all such attempts are on a trial-and-error basis, particularly when the donor leukocytes are unavailable for prognostic in vitro testing. Because we did not have donor lymphoid tissue in any of the liver weaning cases, we attempted to test recipient responsiveness to cells homozygous to the donor DR antigens as described by Reinsmoen et al. (6). A trend was noted of antidonor responsiveness in the rejection group and nonresponsiveness in patients successfully weaned, but this was imprecise. It has been pointed out before that even in vitro testing with donor cells does not correlate well with tolerance in animals (15–17) and humans (18,19). This fundamental limitation of in vitro testing, rather than inherent imperfections in the surrogate technique of homozygous typing, shows that more predictive methods need to be developed.

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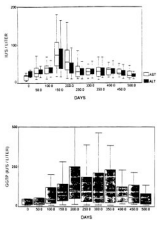

FIGURE 1.

(Top) Changes in AST, ALT vs. days postweaning for the rejection group. Enzyme values are in international units/L. Individual boxes: (line) = median: (boxes) = interquartile range; (bars) = true range, (Bottom) Changes in GGTP vs. days postweaning for the rejection group. Enzyme values are in international units/L. Individual boxes: (line) = median; (boxes) = interquartile range; (bars) = true range.

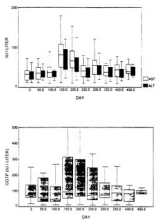

FIGURE 2.

(Top) Changes in AST, ALT, and GGTP vs. days postweaning for the enzyme elevation group. Enzyme values are in international units/L. Individual boxes: (line) = median; (boxes) = interquartile range; (bars) = true range, (Bottom) Changes in GGTP vs. days postweaning for the enzyme elevation group. Individual boxes: (line) = median; (boxes) = interquartile range; (bars) = true range.

TABLE 1

Total patients weaned (n=59)

OLTX No.	Diagnosis	Baseline immunosuppression	Predominant Preweaning complications	Present Lab.: AST/ALT/GGTP	Present status
0133	Hepatitis B	AZA/PEED	Hepatitis, warts	22/29/199	Off
0046	Biliary atresia	AZA/PRED	Osteoporosis, warts	27/31/-	Weaning
0140	Biliary atresia	AZA/PRED	Cholangitis, warts	24/19/119	Rejection
0064	Biliary atresia	AZA/PRED	Squamous cell skin CA, warts	63/49/98	Off
0281	Biliary atresia, Alagilles syn.	AZA/PRED	EBV infection, warts	27/31/16	Off
0325	Biliary atresia, Alagilles syn.	AZA/PRED	EBV infection, warts	31/267-	Off
0166	PBC[a]	AZA/PRED	CMV infections, warts	35730/71	Rejection
0144	PBC	AZA/PRED	Osteoporosis	32/33/24	Off
0042	Wilson's disease	AZA/PRED	Squamous, basal cell skin CA, warts	49/47/47	Off
0105	PNC-C	AZA/PRED	Obesity	37/31/54	Off
0190	Biliary atresia	CsA/PRED		22/30/55	Rejection
0666	Non A, non B hepatitis	CsA/PRED	HTN,RD	38/23/171	Weaning
0194	HCC	CsA/PRED	HTN,RD	45736/110	Rejection
0173	Secondary biliary cirrhosis: trauma	CsA/PRED	Basal cell CA	49/29/481	Rejection
0210	CAH, autoimmune	CsA/PRED	Ulcerative colitis, HTN, sclerosing cholangitis, anemia, RD, warts	38/36/41	Weaning
0488	Hepatitis B	CsA/PRED		42/32/28	Rejection
0171	CAH	CsA/PRED	Warts, osteoporosis	64/56/46	Weaning
1464	PNC-E	CsA/PRED	Steatosis, RD, HTN	28/24/45	Weaning
0605	PNC-C, ? CAH	CsA/PRED	Osteoporosis, HTN, RD, warts	24/28/23	Rejection
0177	Cirrhosis: postnecrotic, Non A, non B hepatitis	CsA/PRED		23/27/82	Rejection
0476	Cystic fibrosis	CsA/PRED	Pulmonary infection	49/33/75	Weaning
0450	Wilson's disease	CsA/PRED	Warts	33/26727	Rejection
0314	Biliary atresia	CsA/PRED	Warts	99/66/-	Weaning
1182	Hepatitis	CsA/PRED	Obesity	20/24/55	Weaning
0349	Cirrhosis: cryptogenic	CsA/PRED	RD, HTN	29/32/20	Weaning
0535	A-l-A	CsA/PRED	Warts	22/37/59	Weaning
0273	A-l-A	CsA/PRED		13/24/39	Weaning
1713	Hepatitis B, FHF	CsA/PRED	Obesity, Osteoporosis	42/37/40	Weaning

OLTX No.	Diagnosis	Baseline immunosuppression	Predominant Preweaning complications	Present Lab.: AST/ALT/GGTP	Present status
0646	Wilson's disease	CsA/PRED		35736732	Weaning
0142	A-l-A	CsA/AZA	Tuberculosis	22/28/18	Rejection
0331	PBC	CsA/AZA	Osteoporosis, HTN, RD	9/21/65	Weaning
1535	A-l-A	CsA/AZA		48/46/19	Weaning
0592	PBC	CsA/AZA/PRED	Osteoporosis	30/25/43	Weaning
2113	Cirrhosis: cryptogenic	CsA/AZA/PRED	Cycloneuropathy, hemosiderosis, hemodialysis, HTN	45/37/-	Rejection
0440	A-l-A	CsA/AZA/PRED	HTN, osteoporosis	26/30/69	Weaning
1308	Hepatitis C	CsA/AZA/PRED	Pulmonary infection, fatty liver, steatosis	111/83/87	Off
0235	PBC	CsA/AZA/PRED	Warts, osteoporosis	557-/50	Weaning
0297	PBC	CsA/AZA/PRED	Osteoporosis	7/14/16	Rejection
0977	Hemochromatosis	CsA/AZA/PRED	TB infection	15/23/16	Rejection
1604	Biliary atresia	CsA/AZA/PRED	Recurrent CMV	83/79/30	Weaning
0289	Non A, non B hepatitis	CsA/AZA/PRED	Warts	38/48/71	Weaning
0323	A-l-A	CsA/AZA/PRED	Recurrent CMV	32/51/196	Weaning
0531	PBC	CsA/AZA/PRED	Osteoporosis	38/40/21	Weaning
0345	A-l-A	CsA/AZA/PRED	Anal warts	46740/21	Weaning
0223	PBC	CsA	Osteoporosis	13/18/10	Rejection
0202	Wilson's disease	CsA		59/59/256	Off
1215	Halothane hepatitis	CsA	Warts	17/23/26	Weaning
0516	PBC	CsA	CMV infection	35/31/121	Weaning
0191	Biliary atresia	CsA	Recurrent mucocutaneous fungal infections	33/357-	Off
0717	A-l-A	CsA	Warts	25/23/-	Weaning
0355	Biliary atresia	CsA	EBV infection	47/-/53	Off
0189	Biliary atresia	CsA	HTN	33/39/9	Off
0447	Biliary atresia	CsA		39/37/-	Weaning
2134	Biliary atresia, Alagilles syn.	FK506	EBV infection	48/37/21	Weaning
3011	Biliary atresia	FK506	Herpes stomatitis	24/44/12	Rejection
0474	Hepatitis B	FK506	Steroid intolerance	134/220/453	Off
2743	Biliary atresia	FK506	HTN,RD	49/267-	Off
2621	Biliary atresia	FK506	Steroid intolerance	75/42/9	Off
3039	A-l-A	FK506	Epigastric pain, peptic ulcer of pylorus, pyloric bulb	54/48/17	Off

[a] HTN = hypertension: RD = renal dysfunction; PNC = postnecrotic cirrhosis; PBC = primary biliary cirrhosis; HCC = hepatocellular carcinoma; A-1-A = alpha 1 antitrypsin; PNC-C = postnecrotic cryptogenic cirrhosis.

TABLE 2

Patients having enzyme elevations without rejection (n=20)

OT No.	Diagnosis	Status	Liver biopsies
2134	Biliary atresia, Alagilles syn.	Weaning	NA[a]
0666	Non-A, Non-B	Weaning	(No ACR) Lobular reactivity
0592	PBC	Weaning	(No ACR) Lobular reactivity
0440	A-l-A	Weaning	NA
1308	Hep. C	Off	Minimal lobular reactivity
0202	Wilson's disease	Off	Large duct obstruction
0235	PBC	Weaning	NA
0064	Biliary atresia	Off	(No ACR) Regenerative hyperplasia ?Drug effect
0042	Wilson's disease	Off	NA
0105	PNC-C	Off	Lobular reactivity
1464	PNC-E	Weaning	NA
1604	Biliary atresia	Weaning	NA
0289	Non-A, Non-B	Weaning	NA
0331	PBC	Weaning	Lobular reactivity
0476	Cystic fibrosis	Weaning	Minimal changes (normal)
1215	Halothane hepatitis	Weaning	NA
0314	Biliary atresia	Weaning	NA
0474	Hep. B	Off	Hepatitis
0516	PBC	Weaning	Lobular reactivity
1182	Hep.	Weaning	Hepatitis

[a] NA = not available.

TABLE 3

Effects of immunosuppression reduction

Weaned patients		Outcome		
Complication	**Number**	**Improved**	**No change**	**Worse**
Infections	7	5	2	
Tumor	2 (SCC)	1[a]	1	
Obesity	1	1[a]		
Hypertension	2		1	1
Osteoporosis	1		1	
Steroid intolerance	3	3		

[a] Dramatic improvement.

TABLE 4

Present status of patients by baseline immunosuppression[a]

Drug(s)	Mean years alter OLTX	Rejection group	Off group	Weaning group
AZA/PRED[b]	16.0±4.3	2	7	1
CsA/PRED[b]	10.2±2.7	7	0	12
CsA/AZA	10.9±5.1	1	0	2
CsA/AZA/PRED	8.6±2.3	3	1	8
CsA	9.7±2.8	1	4	4
FK506	5.4±1.8	1	4	1
Total		15	16	28

[a] Mean years posttransplant of total population (n=59): 10.25±4.3.

[b] X^2=6.77, P<0.01, and Fisher's exact test P=<0.01.

TABLE 5

Homozygous typing cell assay results (n=26)[a].

A. Reactive

OT No.	Baseline immunosuppression	Status	Wean-present state(days)[b]
142	CsA/AZA	Rej.	105
162	AZA/PRED	Rej.	170
166	AZA/PRED	Rej.	142
223	CsA	Rej.	154
235	CsA/PRED/AZA	Weaning	480
297	CsA/PRED/AZA	Rej.	66
1713	CsA	Weaning	330
2134	FK506	Weaning	450

B. Hyporeactive

OT No.	Baseline immunosuppression	Status	Interval Wean-present state (days)[c]	DR antigen (donor)
064	AZA/PRED	Off	109	DR-4
189	CsA	Off	202	DR-7
191	CsA	Off	294	DR-3
1308	CsA/PRED/AZA	Off	84	DR-6
281	AZA/PRED	Off	75	DR-7
194	CsA/PRED	Rej.	56	DR-5
1215	CsA	Weaning	420	DR-7
977	CsA/PRED	Rej.	348	DR-4

[a] The assay was performed in 10 additional patients with equivocal results = (low or unresponsive to all panels including self and 3rd party).

[b] Mean of all rejection patients 146±94.5.

[c] Mean of all off patients 192±163.4.