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Risks and Benefits of Weaning Immunosuppression in Liver Transplant Recipients: Long-Term Follow-up

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THE MORBIDITY arising from the chronic use of anti-rejection medications is an incentive to establish the lowest possible level of immunosuppression necessary to maintain stable graft function. The finding that freedom from immunosuppression was sporadically possible in long-surviving recipients of liver allografts and the concurrent evidence that chimerism was uniformly demonstrable in such tolerant patients[1] have led to a prospective trial of complete drug weaning. In our initial experience, it was shown that significant reductions in medication or their discontinuance could be safely accomplished in liver,[2] and even in a handful of living-related kidney recipients who have been drug free for as long as 30 years.[3] However, the danger of consequent allograft rejection has not been completely assessed and guidelines for judicious weaning need to be clarified. We present here further follow-up on our previously reported weaning trial in liver allograft recipients[2] and results from additional patients subsequently entered.

METHODS

Case Material

We report 95 patients whose weaning was begun between June 1992 and April 1996 after meeting the following criteria: (1) >5 years post-transplantation; (2) >2 years without a documented rejection episode; (3) evidence of medical compliance; (4) availability of cooperative local physician for follow up; (5) absence of acute or chronic rejection on baseline liver biopsy; and (6) exclusion of other diagnoses such as vascular or biliary tract complications or recurrence of original disease. Thirty-one patients were under age 20 at the time of weaning and 64 were between 21 and 68 years of age.

Original recipient diagnoses included viral hepatitis (n = 13), biliary atresia (n = 25), autoimmune hepatitis (n = 4), primary sclerosing cholangitis or primary biliary cirrhosis (n = 16), hepatoma (n = 4), and a miscellaneous group (n = 33) that included alcoholic cirrhosis, cryptogenic cirrhosis, Budd–Chiari, toxic or secondary biliary cirrhosis, Wilson disease, hemochromatosis, α-1 anti-trypsin deficiency, polycystic liver disease, and cystic fibrosis. All were recipients of isolated liver allografts, except for 2 patients who also received a simultaneous kidney graft from their liver donor.

Baseline Immunosuppression

Immunosuppression at the start of weaning consisted of azathioprine (AZA)/prednisone (PRED) in 13 cases, cyclosporine (CyA)/PRED in 32, Cya/AZA/PRED in 24, CyA/AZA in 4, CyA alone in 11, tacrolimus (TAC) in 8, TAC/PRED in 1, and TAC/AZA in 2.

Complications of Immunosuppression

Complications of long-term immunosuppression present at the initiation of weaning included hypertension (n = 32), renal insufficiency (n = 27), skin lesions or malignancy (n = 12), neurologic symptoms or findings (n = 4), infection (n = 6), steroid-related complications (n = 9) such as obesity, growth failure, and bone disease, and diabetes (n = 9). Thirty-seven patients had multiple complications attributable to their immunosuppression.

Weaning Protocol

At the beginning of the prospective trial,[2] AZA was the first drug weaned when it was part of triple drug therapy. Before complete PRED weaning, corticotropin stimulation testing was done to detect adrenal insufficiency. The baseline immunosuppressive agent CyA, AZA, or TAC (Prograf) was then withdrawn by 25% increments at 1 to 2 month intervals as long as hepatocellular enzyme results remained stable. Beginning in 1994, the rate of weaning was slowed and the order of drug discontinuance altered with emphasis on primary reduction of maintenance CyA or TAC with very slow subsequent attention of PRED and AZA (if this was part of the regimen).

Monitoring. Liver injury tests consisting of AST, ALT, GGTP, and serum bilirubin were monitored weekly after changes in drug dosage. A liver biopsy was obtained if liver function abnormalities developed. Treatment for documented cellular rejection consisted of return to the medications preceding the last dose reduction with or without pulse steroid therapy. A switch to tacrolimus therapy in patients previously on other baseline therapy was reserved for moderate or severe ACR or evidence of developing chronic rejection.

RESULTS

Graft Loss and Patient Survival

Two patients died during the study period from non-liver allograft related causes, both with normal liver function.

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Table 1. Prospective Weaning Trial Results (n = 95)

	Off Drugs	Weaning in Progress	Rejection	Weaning Interrupted*
Number of patients (%)	18 (19)	37 (39)	28 (29)	12 (13)
Years from transplant to weaning start				
mean ± SD**	8.3 ± 5.4	8.1 ± 4.2	8.9 ± 3.4	8.5 ± 6.0
median (range)	7.6 (1.8–21.6)	7.8 (1.7–21.3)	8.7 (3.1–19.6)	6.7 (1.8–25.0)
Time from weaning to off, rejection or weaning interruption (mo)		Not Applicable		
mean ± SD	5.9 ± 5.9		13.2 ± 11.6	12.0 ± 8.3
median (range)	0.28 (0–31.7)		9.4 (0.4–42.5)	9.5 (2.6–27.2)
Follow-up (mo)				
mean ± SD†	34.5 ± 11.2	33.6 ± 18.1	22.8 ± 14.4	
median (range)	35.5 (10.1–57.2)	19.6 (1.1–66.2)	25.3 (0.2–42.4)	

*Because of noncompliance (n = 8), recurrent disease (PBC, n = 2), pregnancy (n = 1), and renal failure requiring renal transplant (n = 1).
**P = .901 (ANOVA).
†As of 5/6/96 or patient death.

The first who was still weaning died from septic pulmonary complications of cystic fibrosis. The second patient, who had been returned to baseline immunosuppression following an easily controlled mild acute cellular rejection, died from a pulmonary embolus following complications from a severe toe nail infection. It is noteworthy that these deaths were directly or indirectly attributable to the morbidity of chronic immunosuppression which the weaning protocol was designed to ameliorate. There were no other graft losses.

Status of Prospective Weaning

Table 1 depicts the current status of the 95 patients prospectively weaned. The status of weaning is as follows.

Complete. Eighteen (19%) of the 95 patients in the prospective cohort have been drug free for 0.84 to 4.8 years. Seven of these recipients already were on low levels of immunosuppression at the first visit to the weaning clinic and had drugs stopped at that time. The 11 others were weaned over a mean period of 6.6 months.

In Progress. Currently 37 patients are in the uninterrupted process of drug weaning. The mean percentage decrease in drug dosing from baseline in these patients is 13% of AZA dose, 30% of CyA dose, 14% of prednisone dose, and 44% of the tacrolimus dose.

Interrupted by Rejection. Eighteen patients had weaning interrupted because of histopathologically confirmed rejection, 7 more because this diagnosis was suspected although not proved, and 3 because of suspicion of incipient chronic rejection.

Withdrawal From Protocol. Twelve patients were withdrawn from the protocol due to noncompliance (n = 8), pregnancy (n = 1), renal failure requiring kidney transplantation (n = 1), and recurrent disease (PBC) (n = 2). The 8 excluded because of noncompliance were left at whatever level of treatment had been reached at the time the decision to stop weaning was made. All 8 are well.

Results by Immunosuppression Regimens

There was no significant difference in the prospective trial in the rate of success when the baseline immunosuppressant was tacrolimus or azathioprine. However, there was a difference between these groups and all of the cyclosporine-based regimens ($P < .003$). Azathioprine/prednisone-based patients were more likely to be off drugs at one year as compared to cyclosporine-based patients ($P = .0007$, log rank). Tacrolimus-based patients had a similar advantage ($P = .0031$, log rank).

Impact on Preexisting Complications

The drug-free patients (n = 18) did not have a significant change in renal function or an improvement in hypertension. The most common benefits were resolution of gingival hyperplasia in 2 children, resolution of infections in 3, resolved lymphoproliferative disorders in 3, and relief of neuro-psychiatric complaints in 2.

Six drug free patients completed a short-form health survey[4] assessing 8 areas of patient well-being including physical function, general health, emotional health, and social functioning. When compared with age-matched transplant recipients on immunosuppression more than 5 years after transplant, survey scores were significantly higher in this small group of patients off drugs (K. Ringeride, personal communication).

Allograft Related Adverse Events

Significant hepatocellular enzyme elevations (AST, ALT, GGTP) occurred in 44 prospectively weaned patients during the study period, followed by liver biopsy in 37. The biopsy findings were: acute cellular rejection (n = 18), chronic duct injury (n = 3) not severe enough to meet criteria of chronic rejection (see below), hepatitis (n = 3), normal pathology (n = 7), evidence of biliary tract obstruction (n = 3), non-specific portal inflammation (n = 2), and steatosis (n = 1).

Table 2. Current Status After Two Additional Years of 19 Previously Reported Patients[2] Who Had Enzyme Elevations During Weaning Without a Definitive Explanation

OT#	Diagnosis	Biopsy at First Enzyme Elevation	Follow-up Therapy (interval)	Current Status*
2134	BA	Normal	Normal	Off drugs
0666	NANB Hepatitis	Lobular reactivity	Hepatitis (23 mo)	Weaning
0592	PBC	Lobular reactivity	NA	On drugs
0440	A-1-A	None	NA	On drugs
1308	Hepatitis C	Lobular reactivity	Moderate ACR (23 months)	On drugs
0202	Wilson's disease	Bile duct obstruction	NA	Off drugs
0235	PBC	None	NA	Weaning
64	BA	Regenerative hyperplasia	Early duct injury (19 months)	On drugs
0042	Wilson's disease	None	NA	Off drugs
0105	Cryptogenic	Lobular reactivity	NA	Off drugs
1464	Alcoholic Cirrhosis	None	ACR (4 mo)	Off drugs
0289	NABA Hepatitis	None	Hepatitis (6 mo)	Weaning
331	PBC	Lobular reactivity	Chronic duct injury (8 mo)	On drugs
476	Cystic fibrosis	Normal	NA	Died during weaning**
1215	Halothane hepatitis	None	NA	Off study; pregnancy
314	BA	None	Hepatitis (6 mo)	Weaning
474	Hepatitis B	Hepatitis	NA	On drugs
516	PBC	Lobular reactivity	Recurrent PBC (15 mo)	On drugs
1182	NANB Hepatitis	Hepatitis	NA	On drugs

*Eighteen surviving patients are all clinically well with good or completely normal liver function.
**Pulmonary infection associated with cystic fibrosis.
Abbreviations: NA = not available; BA = biliary atresia; PBC = Primary biliary cirrhosis; A1-A = Alpha-1 Anti-Trypsin deficiency.

Acute Cellular Rejection (n = 18). The biopsy proved acute cellular rejections documented in 18 patients occurred at a mean time of 13.2 months after weaning was started. The characteristic mononuclear cell infiltrate was mild in most cases as was reflected in the fact that only one recipient had an increase in serum bilirubin. There was no significant difference in the laboratory trends of AST/ALT/GGTP in the proved rejection group (n = 18) versus the weaning (n = 37) group.

Treatment consisted of pulse steroids and resumption of the baseline medication schedules in 15 patients, with prompt return of hepatocellular function to normal. The other 3 patients, all on CyA-based regimens, were converted to tacrolimus therapy because of a moderate acute rejection on biopsy, including the one who developed jaundice 29 months after all drugs were stopped. OKT3 was not given to any of the 95 patients in the trial. One patient developed herpes stomatitis following treatment for rejection. Otherwise there were no infectious complications following resumption of anti-rejection therapy.

Unconfirmed Acute Cellular Rejection (n = 7). This group included 4 of the 7 patients who did not undergo biopsy before intensifying immunosuppression, and 3 whose current biopsy revealed only early chronic duct injury that was unchanged from findings in the baseline biopsies (before weaning). Because there was normalization of liver injury tests after the increase of immunosuppression, these 7 cases were arbitrarily included in the acute rejection category.

Suspected Chronic Rejection (n = 3). This diagnosis, which is defined as greater than 50% bile duct loss or obliterative arteriopathy[9] was not made in any of the 95 patients. However, allografts developed de novo histopathologic evidence during weaning of low-grade bile duct injury, prompting restoration of the previous level of immunosuppression in 2 cases, and conversion to tacrolimus in the third.

Viral Hepatitis (n = 3). Two patients developed biopsy evidence during weaning of recurrent hepatitis attributable to Non-A Non-B virus (later shown to be Hepatitis C). A third recipient whose original disease was biliary atresia, developed de novo C virus hepatitis infection. Weaning has continued in these patients with stabilization of liver injury tests.

Recurrent Autoimmune Disease (n = 2). Two patients who were 7 and 8 years post-transplantation when they entered the study, were diagnosed with histopathologically obvious recurrent primary biliary cirrhosis 7 and 24 months after the initiation of weaning. Liver function tests normalized after return to the preexisting CyA-based baseline immunosuppression, including prednisone. There has been no recurrence of autoimmune hepatitis in this series.

Bile Duct Obstruction (n = 3). The liver function abnormalities in all 3 patients were incorrectly attributed to rejection and briefly treated as such in 2 cases. Liver enzyme values normalized in all 3 recipients after bile duct decompression and weaning was resumed.

Previously Reported Equivocal Cases

In our report 2 years ago of the first portion of the current prospective series, there were 19 liver recipients whose reasons for enzyme elevations during weaning were not considered to be unconditionally established.[2] In the inter-

vening 2 years, 10 of these patients have had progression of the suspected pathologic process (bolded patients, Table 2); 5 have remained unchanged with continuation or completion of weaning, one died from pulmonary complication of cystic fibrosis and 3 were withdrawn from the protocol.

DISCUSSION

The rationale for post-transplant drug weaning rests with recent evidence suggesting that the leukocytes (including stem cells) contained in organs migrate after transplantation and produce persistent chimerism which is essential for sustained survival of the allografts.[1] We have emphasized that chimerism is not the same as tolerance.[1,5] Chimerism and the derivative state of tolerance (if it is achieved) are almost contemporaneous in numerous rodent models of liver transplantation, many of which do not require immunosuppression.[6] In contrast, the cause (chimerism) and the effect (tolerance) are separated by months or years when liver transplantation is performed in outbred animals and humans no matter what the means of immunosuppression.[7] The duration of this critical period must be determined at present by trial and potential error. Although many liver recipients have stopped immunosuppression, the desired drug-free end-point may never be achieved in some patients whose chimerism (and organ allografts) can nevertheless be maintained for a lifetime under continuous immunosuppression. The error has been pointed out[1,5,7] of believing that either the presence or the quantity of donor leukocyte chimerism can be used per se to guide decisions about drug weaning.[8–10]

The majority of the patients entered into the trial had been kept at a maintenance level of immunosuppression higher than was needed. Even those patients who developed rejection during the weaning process are receiving less average immunosuppression than when they started. The potential benefits of weaning are too obvious to enumerate. Consequently, our emphasis in this report has been on the incidence of rejection which was proved to have occurred acutely at some time during or after weaning in at least 18 (19%) of the 95 patients entered. Seven more unverified cases were placed in the acute rejection category including 3 in which biopsy only revealed minor duct injury. Including these 7 patients whose restoration of immunosuppression to preexisting levels resulted in a clinical response, there was a 25 of 95 (26%) incidence of acute rejection which occurred from 0.2 to 42 months after starting the weaning, and no unequivocal examples of chronic rejection. All but 3 of the rejections were classed as minimal to mild, necessitating only restoration of the previous baseline treatment. However, the rejection was histopathologically moderate or severe in the exceptional cases and 1 of these patients became jaundiced with a peak bilirubin of 12 mg%. All 3 were rescued with tacrolimus.

The trial was not marred by any examples of chronic rejection, at least by the criteria conventionally used to make this diagnosis.[11] However, when 3 patients developed low grade de novo histopathologic findings of duct injury suggestive of incipient chronic rejection, immunosuppression was restored to preexisting levels (n = 2) or replaced with tacrolimus (n = 1).

The practical lessons from this experience deserve strong emphasis. One is the absolute necessity of close physician surveillance with frequent assessments of liver function, repeat biopsy with the slightest suspicion of rejection, and prompt restoration of immunosuppression if this is the diagnosis (which it frequently is not). In addition, weaning should not be as abrupt as was done in the early patients of this series or in the trial of Sanborn et al.[12] The risk of recurrent autoimmune disease was previously discussed in our earlier report.[2] Although recurrence of autoimmune hepatitis has not yet been observed, 2 patients with PBC developed recurrence, raising the question whether attempts to completely wean such patients should be made.

With these provisos, our conclusion is that drug weaning is an important management consideration for a large number of stable, long-surviving liver recipients. Weaning apparently can be safely carried to completion in a significant percentage of this population in which complications of immunosuppression have been the principal cause of late death.[1] However, the long term benefits of drug reduction or discontinuation need to be continually measured and balanced against the risk of drug withdrawal. The risk can be minimized by careful management and timely intervention when called for. Finally, the experience in this study has emphasized the frequency with which late hepatic allograft dysfunction is due to causes other than rejection.[13]

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