

# Conversion From Tacrolimus to Cyclosporine-A Based Immunosuppression Following Liver Transplantation

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We examined the frequency, reasons and outcome after conversion from Tacrolimus to Cyclosporine A.

From August 1989 to December 1992, 1000 consecutive liver transplantation patients were studied, which included 834 adults (age >18 yr.) and 166 children with mean follow-up of 77 months (range 56 to 96). A prospectively populated electronic database was queried to identify patients that underwent conversion, the clinical indication and outcomes.

Thirty-seven out of 834 adult recipients (4.43%), mean age of  $48.4 \pm 12.9$  years, 19 male (51.35 %) and 18 females (48.64%) required conversion from Tacrolimus to Cyclosporine A baseline immunosuppressive therapy. No pediatric patient required conversion. The mean time interval from liver transplantation to Cyclosporine A conversion was  $443.45 \pm 441.44$  days (range 22 to 1641). The clinical indications for conver-

sion included: 20 neurological (54%), 6 gastrointestinal (16%), 5 hematological (14%), and 6 other (16%) scenarios. Seven of the 37 patients (18.9%) died. The causes of death were multi-organ failure (2), sepsis (2), pancreatitis (1), hepatic failure due to relapse of ethanol abuse (1), and unknown cause (1). Nine out of 37 patients (24.32%) had to be reconverted to Tacrolimus (mean  $282.22 \pm 499.79$  days; range 15 to 1583 day with a median of 135) after institution of Cyclosporine A; none showed recurrence of the original symptoms. The reasons for these re-conversions were acute cellular rejection (44%, n=4), chronic rejection (11%, n=1), increased hepatic enzymes (33%, n=3) and progressively worsening neurological symptoms (11%, n=1).

The frequency of conversion from Tacrolimus to Cyclosporine A was 4.43%. Conversion is safe and efficacious if done in a controlled setting. Additionally, re-conversion to Tacrolimus for lack of efficacy of Cyclosporine A did not appear to be associated with a recurrence of the condition that caused the initial switch.

**Keywords:** Calcineurin inhibitor, neurotoxicity, nephrotoxicity, bone marrow, gastro-intestinal tract.

Tacrolimus (TAC) was introduced into clinically trials as a primary immunosuppressive agent in August 1989 and, subsequently, has proven to be a

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more potent agent than cyclosporine (CsA). Its mechanism of action as an immunosuppressive agent is by the inhibition of interleukin-2 production with an estimated 100 times more efficacy as such than CsA [1]. The rates of acute cellular rejection, graft and patient survival after liver transplantation (LTX) have been reported to be more favorable with the use of TAC-based immunosuppression [2-6]. However TAC is also associated with side effects that may require consideration of conversion to other immunosuppressive-based regimens. Among the most common reported side effects of TAC is neurotoxicity, which can manifest itself in a variety of presentation: lethargy, anorexia, behavioral changes, depression, tremor, headache, insomnia, nightmares, vertigo, dysarthria, mood changes, photophobia, akinetic mutism (expressive aphasia), seizure disorders, psychosis, encephalopathy, movement disorders, delirium, coma, cerebral pontine myelinolysis, cortical blindness, deterioration in cognitive function, pseudo bulbar paralysis, chorea, nystagmus, polyneuritis, and stupor have all been reported [7-10]. Moreover, nephrotoxicity [11, 15], gastrointestinal toxicity [12], hematological effects [13], hyperglycemia [14], hypertension [15], hyperkalemia are ascribed toxicities with variable incidence. Even though the side-effect profile of CsA [15-22] overlaps with TAC, conversion from TAC to CsA provides an ability to test whether a given individual condition might be idiosyncratic or affected by the pharmacokinetic peculiarities of a given calcineurin inhibitor for an individual patient. The aim of the present study was to examine the incidence of the conversion from TAC to CsA in a primary LTX population, the reason for the conversion and the outcome after conversion.

## Material and Methods

This is a retrospectively reviewed single-center study based on data collected on a population of patients who underwent, after obtaining informed written consent, LTX between August 1989 to December 1992. One thousand consecutive transplanted patients were evaluated for this study; the demographics of this population have been well described [6]. Of these 834 were performed in adults (age > 18 years) and 166 were performed in pediatric patients. All patients were treated with intravenous TAC in the immediate postoperative period with a dose of 0.05 to 0.15 mg/kg/day. Prior to the advent of whole blood monitoring, TAC therapeutic drug monitoring targeted plasma trough levels in the range of 1.0-2.5 ng/ml (equivalent to whole blood levels of 8-15 ng/ml). Upon resumption of gastro-intestinal function post transplantation, the intravenous route was substituted with oral TAC doses to maintain similar target levels. The LTX population that made up this study consisted of 37 patients of the 834 (4.43%), mean age of  $48.4 \pm 12.9$  years, 19 males (51.35 %) and 18 females (48.64%), no pediatric patients required conversion. All patients were followed and had a mean follow-up of 77 months (range 56 to 96 months). Profiles of rejection, safety parameters, levels of immunosuppression, evidence of disease recurrence, and physiologic disturbances were evaluated using a prospective designed clinical database (EDIT, Electronic Database Interface for Transplantation, Pittsburgh, PA). This study was approved by the University of Pittsburgh Institutional Review Board.

## Results

### Indications and Response to Conversion

In this series, conversion from TAC to CsA was triggered by neurological symptoms in 20 patients (54%), gastrointestinal complaints in 6 (16%), hematological alterations in 5 (14%), and other reasons in 6 (16%). The pediatric population appeared to tolerate TAC better than adults (23-24) since no pediatric patient in this series required conversion. The mean interval for conversion from TAC to CsA was  $443.45 \pm 441.44$  days (range 22 to 1641). There did not appear to be any correlation between the incidence of complications and the indications for LTX, which reflected the overall makeup of LTX recipients. In general, the levels of TAC at the time of conversion were at the lower end of the therapeutic range (data not shown). The majority of the patients demonstrated clinical improvement after the switch in the baseline-immunosuppressive agent.

### Neurological Indications

Details of the 20 patients who experienced neurological symptoms are shown in (Table 1.) These symptoms occurred at a median of 146 days after LTX (range 22 – 1305 days). The primary presentation included 7 cases of confusion, 4 cases of lethargy, 2 cases each of severe tremors, seizures, dysarthria/aphasia and intractable headaches, and 1 case of depression. Fifteen patients who developed neurological symptoms underwent imaging studies, inclusive of either MRI and/or CT scan of the brain, as well as an EEG, in order to exclude the presence of CNS lesions. Eleven patients were studied initially with a CT scan of the head. These studies were all negative for ischemia, hemorrhage or tumor. Eight patients had an MRI of the head, and in three cases this followed an inconclusive head CT scan. The most

**Table 1.** Demographics of patients converted to cyclosporine for neurological symptoms after liver transplantation

Case #	Age	Sex	Diagnosis	Days Post-LTX	Symptoms	Outcome
1	58	F	PNC-E/HCV	51	Tremor	I <sup>a</sup>
2	49	F	HBV	814	Confusion	I
3	52	M	HCV/HCC	65	Confusion	I
4	38	F	PBC	328	Lethargy	I, R <sup>b</sup>
5	46	F	HCV	365	Headache	I
6	38	F	FHF	106	Confusion	I, R, RC <sup>c</sup> , D <sup>d</sup>
7	37	F	HCV	730	Confusion	I
8	40	M	PNC-E	719	Headache	I
9	45	F	PBC	485	Lethargy	I
10	60	F	HCV/HCC	82	Confusion	I
11	65	M	HBV	173	Seizures	NI <sup>e</sup> , D
12	69	M	HBV	119	Confusion	NI, D
13	63	M	HCV	102	Depression	I, R
14	37	F	PNC-E	674	Dysarthria	NI, RC, D
15	52	M	A1 HEP	1305	Seizures	I
16	61	M	PNC-E	22	Confusion	I
17	43	M	HCV	733	Aphasia	NI
18	56	M	PNC-E/HCV	312	Lethargy	I
19	67	F	BUDD-CHIARI	77	Tremor	NI, D
20	66	M	HCV	68	Lethargy	NI, D

**Abbreviations:** a, improved; b, no improvement; c, rejection; d, re-converted; e, died

common finding was parenchymal volume loss, with or without cerebral atrophy, which was observed with an increased frequency in association with confusion. No other significant associations were found.

#### *Gastrointestinal Indications*

In 6 cases (16%), the conversion to CsA was triggered by gastrointestinal complaints (Table 2), which occurred a median of 436.5 days (range 42 - 828) after TAC was initiated. This included 4 cases of anorexia, and 1 case each of malabsorption and gastric hypomotility. In the cases of anorexia, while all four patients experienced improvement after conversion, they subsequently all developed rejection (see below) and three required re-conversion to TAC. The patient with "gastric hypomotility" presented with gastric distention, upper abdominal fullness and occasional episodes of vomiting, he improved after conversion. The patient with "malabsorption" was a young man with PSC and UC, who presented with weight loss, diarrhea and normal caloric intake - he improved significantly after the conversion to CsA.

#### *Hematological Indications*

Five patients (14%) developed hematological alterations following LTX and were converted to CsA at a median of 255 days (range 26 - 1520 days) post-LTX (Table 3). We observed 3 cases of thrombocytopenia, 1 case of anemia and 1 case of ill-defined hemolysis. Four of the patients in this subgroup were on steroids at the time of the conversion to CsA. A double immunosuppressive regimen (CsA/prednisone) was maintained after conversion to CsA-based immunosuppression and resolution of the hematological abnormalities were noted. Therefore, we concluded that steroids

did not play a role in the reversal of the hematological alterations in these patients.

#### *Other Indications*

In the remaining 6 cases (16%), the conversion to CsA occurred at a median of 1002 days (range 155 - 2005 days) after LTX (Table 4). The remaining indications were quite varied and included one case each of reduced immunosuppression for post-transplant lymphoproliferative disease (PTLD) and sepsis, type II diabetes mellitus, and unexplained skin rash. In 2 cases, the patients did not have access to TAC; therefore, they were converted to CsA.

#### **Deaths**

Seven (19%) patients who were converted from TAC to CsA died, however, in no case was the conversion associated with patient death. Two patients died as a result of multi-organ failure, 2 of sepsis, 1 due to pancreatitis, 1 as a consequence of liver failure secondary to recidivism with ethanol abuse, and in 1 patient the cause of death could not be determined because he died at home. When deaths were analyzed by clinical indication for conversion it was noted that 6 of the 7 patient deaths occurred in the group of patients converted for neurological symptoms. No patients converted for either gastrointestinal complaints or hematologic alterations died during the observational period of this analysis. The remaining patient that died fell into the "Other Indications" category - this patient died of multi-organ failure (MOF) 114 days after the switch to CsA who was septic at the time of conversion.

#### **Re-Conversion to TAC**

Nine out of 37 patients (24.3%) were reconverted to TAC at a mean of  $282.22 \pm 499.79$  days after starting CsA (range 15 to 1583) - 4 because of acute

**Table 2.** Demographics of patients converted to cyclosporine for gastrointestinal symptoms after liver transplantation

Case #	Age	Sex	Diagnosis	Days post-LTX	Reason for switch	Outcome
1	56	M	HCV	92	Anorexia	I <sup>a</sup> , R <sup>b</sup> , RC <sup>c</sup>
2	41	M	PNC-E	828	Anorexia	I, R
3	55	F	PNC-E	48	Anorexia	I, R, RC
4	19	M	PSC+UC	545	Malabsorption	NI <sup>d</sup> , R, RC
5	61	F	PNC-E	42	Anorexia	I, R
6	24	M	PSC	767	Gastric hypomotility	I

**Abbreviations:** a, improved; b, rejection; c, re-converted ; d, no improvement

**Table 3.** Demographics of patients converted to cyclosporine for hematologic abnormalities after liver transplantation

Case #	Age	Sex	Diagnosis	Days post-LTX	Reason for switch	Outcome
1	52	M	HCC/HCV	26	Thrombocytopenia	I <sup>a</sup> , R <sup>b</sup> , RC <sup>c</sup>
2	45	F	HCV	1520	Thrombocytopenia	I
3	42	F	PNC-E	255	Anemia	NI <sup>d</sup> , RC
4	23	M	HBV/HCV	189	Hemolysis	I
5	24	F	PBC	256	Thrombocytopenia	I, R

**Abbreviations:** a, improved; b, rejection; c, re-converted ; d, no improvement

**Table 4.** Demographics of patients converted to cyclosporine for miscellaneous reasons after liver transplantation

Case #	Age	Sex	Diagnosis	Days post-LTX	Reason for switch	Outcome
1	46	F	HCV	274	PTLD	I <sup>a</sup>
2	44	F	PNC-E	155	Sepsis	NI <sup>b</sup> , RC <sup>c</sup> , D <sup>d</sup>
3	56	M	HCV	1095	Skin rash	I
4	61	M	HBV	910	Type II diabetes	NI
5	47	F	SBC	2005	Lack of Access	RC
6	49	M	NANB	1520	Lack of Access	I

**Abbreviations:** a, improved; d, no improvement; c, re-converted; e, died

cellular rejection, 1 due to chronic rejection, 2 for no improvement after conversion, and 1 due to progressively worsening neurological symptoms. In one case, the lack of access to TAC was resolved after CsA conversion and the patient resumed TAC. In the cases where re-conversion to TAC was performed due to rejection, reversing the rejection

was successful and without reappearance of the original toxicities that forced conversion.

### Discussion

Since the introduction of CsA, calcineurin inhibitors have been considered responsible for a variety of unusual post-transplant non-immuno-

logic complications. Specifically, these include neurological, gastrointestinal, hematological and other side effects, although in retrospect, many of these events are seen in the general transplant population, regardless of the specific immunosuppressive agent. Metabolic or technical complications, physiologic disturbances and exacerbation of pre-existing conditions are often incorrectly ascribed to the immunosuppressive regimen. In reality, it is difficult to differentiate immunosuppressive side effects from other conditions. For example, HCV as the indication for LTX may be associated with post-LTX depression [25]. In addition, loss of brain volume secondary to alcoholism is well described [26-27], and thus, association of these findings with neurological conditions under any immunosuppressive agent may not be accurate. Nevertheless, in clinical practice, the first reaction to an unusual presentation in the post-transplant period is to focus on the management of the immunosuppressive regimen. By trial-and-error, improvements in these complications may either be due to chance (i.e. improvement regardless of immunosuppressive management), or by intervention (i.e. conversion). In our series of patients, most patients improved with conversion from TAC to CsA when presenting with unusual neurological, gastrointestinal, hematologic or miscellaneous causes. The improvement could have also been due to differences in pharmacokinetic absorption and distribution between the two agents. It has been reported that conversion from CsA to TAC can improve the same spectrum of clinical conditions (ref), and therefore these findings are not unique to the conversion from TAC to CsA. The switch from TAC to CsA has been previously reported [10, 28-29, 32] - in our study, 24

(32%) of the patients required re-conversion from CsA to TAC mainly for acute/chronic cellular rejection. Confirming the concept that TAC itself may not have been the root-cause of these complications, none of the patients re-converted to TAC showed recurrent signs or symptoms, which prompted the first change in the drug regimen. The availability of numerous options for immunosuppression is clearly an advantage over the dependency on CsA-based immunosuppression alone in the 1980's. Conversion to calcineurin-free immunosuppression, such as rapamycin based immunosuppression or mycophenolate mofetil based immunosuppression, has obvious advantages, when there is intolerance to calcineurin inhibiting immunosuppressive agents. The lessons learned from this study are that conversions can be accomplished with good results and safely. In addition, when faced with a difficult clinical situation, conversion may indeed be the cause of, or temporally related to, clinical improvement. Our data also suggests that the more acutely ill patients are at the time of the transplant, and/or affected by alcoholic liver cirrhosis, are more prone to develop side effects with the usage of higher doses of TAC used in the early experience using TAC. We recommend that the first approach to unexplained clinical conditions should include an attempt to decrease the dosage of TAC, and if this fails to consider a switch to CsA.

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