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Treatment of tacrolimus-related adverse effects by conversion to cyclosporine in liver transplant recipients

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Abstract When tacrolimus side effects persist despite dose reduction, conversion to cyclosporine-based immunosuppression (CyA) is necessary. We characterized tacrolimus side effects that warranted discontinuation of the drug, and outcomes after conversion. Of 388 liver recipients who received tacrolimus as primary immunosuppression, 70 required conversion to CyA. We recorded indication for conversion, whether conversion was early or late after transplantation, tacrolimus dose and trough blood level at conversion, and incidence of rejection after conversion. Conversion was early in 29 patients (41.4%) and late in 41 (58.6%). Indications for early conversion were neurotoxicity (20), (insulin-dependent) diabetes mellitus (IDDM) (5), nephrotoxicity (3), gastrointestinal (GI) toxicity (6), and cardiomyopathy (1), and for late conversion were neurotoxicity (15), IDDM (12), nephrotoxicity (3), GI toxicity (5), hepatotoxicity (6), post-transplant lmphoproliferate disease (PTLD) (2), cardiomyopathy (1), hemolytic anemia (1), and pruritis (1). All early-conversion patients showed improvement/resolution of symptoms. Among late-conversion patients, 37 (90.2%) had improvement/resolution; in 4 (9.8%), adverse effects persisted. The overall rejection rate was 30%. Sixty-two patients (88.6%) are alive with functioning grafts 686 ± 362 days (range, 154–1433 days) after conversion. When tacrolimus side effects are unresponsive to dose reduction, conversion to CyA can be accomplished safely, with no increased risk of rejection and excellent long-term outcome.

Key words Tacrolimus toxicity · Liver transplantation · Cyclosporine conversion · Immunosuppression side effects

Introduction

The introduction of cyclosporine (CyA) and tacrolimus significantly improved the results of liver transplantation. Outcomes, however, are still compromised by rejection, infection, and CyA- or tacrolimus-induced adverse effects.

Tacrolimus, a potent immunosuppressive agent, is known to cause a variety of adverse effects, including neuro-psychiatric toxicity [1, 3, 18], nephrotoxicity [17], diabetogenicity [10, 22], gastrointestinal (GI) toxicity [6], and cardiac and other less common toxicities [2, 7]. These adverse effects generally occur early after transplantation. Usually, they are dose-related and controllable with dose adjustment [12]. When side effects persist despite dose reduction, conversion to cyclosporine (Sandimmune or Neoral) is necessary.

In an earlier report, we reviewed the incidence of tacrolimus side effects severe enough to warrant discontinuation of the drug or conversion to CyA [15]. Since tacrolimus was approved by the U.S. Food Drug Administration in 1994, however, there has been no major

analysis of liver recipients intolerant of tacrolimus. In this large, single-center study, we analyzed outcomes in patients converted to CyA for tacrolimus toxicity unresponsive to dose reduction. Furthermore, we sought to determine whether indications for and response to conversion differed between the early post- transplant period, when blood levels of immunosuppressant agents are typically higher, and the later post-transplant period. Finally, we analyzed whether pediatric or elderly recipients were at higher risk of severe toxicity.

Patients and methods

Between June 1994 and December 1997, 595 patients underwent 687 liver transplantations at our center. In the case of 388 patients (331 adults, 57 children), tacrolimus was the primary immunosuppressive agent. These patients received an initial tacrolimus dose of 0.1 mg/kg per day, which was adjusted to maintain a blood level of 15–20 ng/ml during the 1st month after transplantation, 10–15 ng/ml during the 2nd and 3rd months, and 5–10 ng/ml thereafter. In addition, patients received 500 mg IV methylprednisolone after reperfusion. Starting on postoperative day 1, methylprednisolone was tapered from 200 mg to 20 mg within 5 days; thereafter, methylprednisolone was maintained at 20 mg/day and then tapered by 2.5 mg/month to a maintenance dose of 5 mg/day after 6 months post-transplantation. The tacrolimus whole blood level was measured using the IMX monoclonal fluorescence polarization immunoassay technique (Abbott Laboratories, Dallas, Tex.); the suggested therapeutic range is 5–20 ng/ml. When concomitant pharmacotherapy was initiated with agents that might affect cytochrome p450 metabolism, patients' tacrolimus doses were adjusted accordingly.

When patients developed severe tacrolimus-related side effects, the drug was held for 3–5 days and then restarted at a low dose, or the dose was reduced; if side effects persisted or worsened, patients were converted to CyA.

Tacrolimus hepatotoxicity was identified on the basis of criteria described previously by our group [7, 9]. GI toxicity was defined as a chronic presence of at least two of the following signs: nausea, anorexia, diarrhea, or weight loss not attributable to primary GI pathology [6]. Other GI pathology was excluded by appropriate serum chemistries, cultures, endoscopy, and radiologic examination. Post-transplant (insulin-dependent) diabetes mellitus (IDDM) was defined as a fasting blood glucose level of more than 400 mg/dl at any point or more than 200 mg/dl for 2 weeks, or a need for insulin treatment for at least 2 weeks. Uncontrollable IDDM was defined as increasing insulin requirements or patients requiring IV insulin drip in order to control blood sugar in the absence of infectious complications.

In this retrospective study, we identified patients converted from tacrolimus to CyA due to adverse reactions, and recorded age, liver disease, indication for conversion, interval to conversion, and tacrolimus dose (mg/kg) and trough blood level (ng/ml) at conversion. The primary end-point of this study was response to conversion, which was graded as resolved, improved, or unchanged based on the evolution of initial symptoms within 2–3 months.

Patients were divided into two groups based on interval to conversion (early: < 30 days after liver transplantation; late: > 30 days after liver transplantation) in order to determine whether indications for and response to conversion differed between the early post-transplant period, when blood levels of immunosuppressant agents are typically higher, and the later post-transplant period.

We also looked at pediatric (age < 18) and elderly recipients (age > 60) to determine whether these groups showed more tacrolimus-related adverse effects or different toxicity patterns.

In addition, we analyzed the incidence of rejection and steroid-resistant rejection (SRR) as well as graft and patient survival after conversion.

Patients with new-onset IDDM were converted from tacrolimus to CyA when their blood glucose levels rose above 500 mg/dl or when increasing doses of insulin were required.

For statistical analysis, the chi-squared test was used; a P value of less than 0.05 was considered statistically significant.

Results

Of 388 patients on initial immunosuppression with tacrolimus, 70 (18%) were converted to CyA for toxicity. The proportion of liver recipients who initially took tacrolimus for primary immunosuppression and were converted to CyA increased by year: 7 patients (12%) in the second half of 1994, 19 patients (18%) in 1995, 19 (21%) in 1996, and 25 (26%) in 1997. Sixty-one patients were eventually converted to Neoral; 9 patients were converted to Sandimmune. Patient characteristics are summarized in Table 1. Primary indications for early and late conversions appear in Table 2. Neuropsychiatric adverse effects, the most common indication for conversion to CyA, occurred more frequently early after transplantation, in 20 patients (68.9%) in the early group and 15 (36.6%) in the late group ($P < 0.01$). Seventeen recipients required conversion due to IDDM, which was the second leading indication for conversion. Fifteen developed new onset of IDDM; 2 had IDDM before transplantation. All patients required increasing doses of insulin, with unstable blood glucose levels. Although this side effect almost always occurred early after transplantation, the majority of patients were converted to CyA later. Five patients required conversion early after transplantation; 2 had IDDM before transplantation, 1 had new-onset IDDM with uncontrollable blood sugar, and 2 had new-onset IDDM along with neurotoxicities. Six patients in the late-conversion group were hospitalized for blood glucose levels of greater than 500 mg/dl and required IV insulin drip before conversion. Hepatotoxicity, post-transplant lymphoproliferative disease (PTLD), hemolytic anemia, and pruritis related to tacrolimus toxicity developed only in the late period.

Conversion was required within the 1st month after transplantation in the case of 29 patients (41.4%), at a mean of 18 ± 7 days (range, 6–28 days). In 41 patients (58.6%), conversion was required after 30 days post-transplantation, at a mean of 139 ± 147 days (range, 31–668 days). The mean follow-up after conversion was 736 ± 400 days (range, 170–1433 days) in early-conversion patients and 686 ± 362 days (range, 154–1389 days) in the late-conversion group.

Table 1 Patient characteristics ($n = 70$)

	Early group ($n = 29$)	Late group ($n = 41$)
Mean age (years)	48.8 ± 15.8 (range, 7–70)	47.8 ± 21.4 (range, 0–72)
Gender (male/female)	18/11	22/19
Pediatric patients	2	6
Race		
White	18	24
Black	5	7
Hispanic	5	8
Oriental	1	2
Liver disease		
Hepatocellular	17	27
Cholestatic disease	8	10
Fulminant hepatic failure	3	2
Other	1	2

Table 2 Primary indications for early (< 30 days) and late (> 30 days) conversion from tacrolimus to cyclosporine. Some patients showed more than one toxicity (*IDDM* insulin-dependent diabetes mellitus, *GI* gastrointestinal, *PTLD* post-transplant lymphoproliferative disease)

	Early group ($n = 29$)	Late group ($n = 41$)
Neuropsychiatric toxicity	20 (68.9%)	15 (36.6%)
Headache	2 (10%)	5 (34%)
Tremor	5 (25%)	2 (13%)
Insomnia	5 (25%)	1 (7%)
Speech disorder	5 (25%)	1 (7%)
Seizure	3 (15%)	2 (13%)
Psychiatric disorder	12 (65%)	2 (13%)
Peripheral neuropathy	0	2 (13%)
Uncontrollable IDDM	5 (17%)	12 (29%)
Nephrotoxicity	3 (10%)	3 (7%)
GI toxicity	6 (21%)	5 (12%)
Hepatotoxicity	0	6 (15%)
PTLD	0	2 (5%)
Cardiomyopathy	1 (3%)	2 (5%)
Hemolytic anemia	0	1 (2.5%)
Pruritis	0	1 (2.5%)

Tacrolimus doses and levels at the onset of adverse reactions and prior to conversion to CyA are shown in Table 3.

In the early-conversion group, all patients showed resolution or improvement of their symptoms of toxicity (Table 4). In the late-conversion group, 37 patients (90.2%) showed improvement or resolution of symptoms, but adverse effects persisted in 4 patients (9.8%): 1 who was converted to CyA for nephrotoxicity (kidney biopsy revealed chronic advanced glomerulonephritis), 2 who were converted due to hepatotoxicity (1 with recurrent autoimmune hepatitis, and 1 with steatohepatitis), and 1 who was converted for neurologic impairment. Because this last patient could not tolerate CyA, this drug too was stopped and he was started on mycophenolate mofetil. In the patient converted for steatohepatitis, liver function normalized early after conversion, but 1 month later rose again to preconversion levels.

Table 3 Tacrolimus doses and levels at onset of symptoms and prior to conversion to cyclosporine

	Early ($n = 29$)	Late ($n = 41$)
Peak tacrolimus		
Dose (mg/kg per day)	0.12 ± 0.07 (range, 0.02–0.29)	0.11 ± 0.12 (range, 0.03–0.71)
Level (ng/ml)	20.4 ± 8.5 (range, 9.3–49.6)	14.5 ± 9.8 (range, 5.0–55.2)
Last tacrolimus		
Dose (mg/kg per day)	0.04 ± 0.06 (range, 0.0–0.23)	0.03 ± 0.05 (range, 0.0–0.21)
Level (ng/ml)	7.1 ± 2.8 (range, 1.4–12.0)	6.9 ± 3.9 (range, 1.7–18.8)

Table 4 Results of conversion from tacrolimus to cyclosporine and resolution of the symptoms

Symptoms	Early group ($n = 29$)	Late group ($n = 41$)
Resolved	21 (72%)	28 (68.3%)
Improved	8 (28%)	9 (21.9%)
Unchanged	0	4 (9.8%)

Fifty-seven pediatric patients received tacrolimus as initial immunosuppression. Eight (14%) were converted to CyA for neurotoxicity (2), cardiomyopathy (2), hepatotoxicity (2), and PTLD (2). Two children were converted to CyA early after transplantation (7 and 11 days) due to seizure and speech disorder. In 6 cases, conversion was done more than 30 days after transplantation. All pediatric patients responded to conversion with a resolution of side effects.

Overall, 18 patients (25.7%) who required conversion to CyA were over 60 years of age. Neurotoxicity was the leading indication for conversion in elderly patients; 4 of 6 elderly patients (66.7%) in the early group and 6 of 12 (50%) in the late group were converted to CyA for this indication. The incidence of neurotoxicity in the elderly patients was similar to that in adults under 60 years of age: 13 of 21 (61.9%) in the early group and 8 of 23 (34.8%) in the late group (P = NS). Except for the one patient described above who could not tolerate CyA after conversion and who was switched to mycophenolate mofetil, all patients with neurotoxicity improved regardless of age or time of conversion.

The overall rejection rate in patients converted to CyA was 30% (Table 5). The mean time to rejection in converted patients was 134 ± 243 days (range, 2–825 days). The rejection rate was higher in the early-conversion group than in the late-conversion group

Table 5 Comparison of rejection episodes between early- and late-conversion groups (*SRR* steroid-resistant rejection)

	Early group ($n = 29$)	Late group ($n = 41$)	Overall ($n = 70$)
Acute episodes	16	13	29
Patients with rejection[a]	13 (44.8%)	8 (19.5%)	21 (30%)
SRR	1 (3%)	1 (2%)	2 (3%)

[a] $P < 0.025$ (patients with early rejection vs patients with late rejection)

Table 6 Cause and time of death in patients converted to cyclosporine

Cause of death ($n = 10$)	Days after conversion
Chronic rejection	709
Sepsis	
Biliary ($n = 2$)	346, 95
After hip surgery	293
Respiratory	140
Recurrent autoimmune hepatitis	226
Recurrent hepatitis C ($n = 3$)	305, 647, 670
Nocardiosis	27

(44.8 vs 19.5%) ($P < 0.025$). On the other hand, 4 patients in the early group had acute rejection episodes less than 7 days after conversion. Only 2 patients developed SRR; both responded to OKT3. One patient developed chronic rejection due to noncompliance.

Ten deaths occurred among patients who were converted to CyA. Causes of death are shown in Table 6. Of the converted patients, 60 (85.7%) are alive with functioning grafts at 705 ± 382 days (range, 154–1433 days) after conversion.

Discussion

The introduction of tacrolimus in liver transplantation has resulted in a decreased incidence of graft rejection [8]. Tacrolimus has also been successfully used in the treatment of chronic rejection, as rescue therapy for SRR, and as an alternative immunosuppressant for treatment of CyA-related adverse effects [8, 16, 19, 20]. Tacrolimus is associated with numerous side effects many of which, however, are similar to those of CyA. In some cases, these side effects can be severe and unresponsive to dose reduction. Among our patients, the incidence of conversion to CyA for tacrolimus-related side effects was 18%. This rate is similar to that found in a multicenter study of patients given rescue therapy with CyA because they were intolerant of tacrolimus [4].

In our study, the leading indication for conversion to CyA was severe neuropsychiatric adverse effects, which occurred in 35 patients (50%), most often early after transplantation. Among the neuropsychiatric adverse effects, severe tremor, insomnia, speech disorders, seizure, paranoia, and hallucination were more often encountered early, while severe headaches and peripheral neuropathies were more frequently seen later. Neurotoxicity was the leading indication in previously published series [3, 18]. Burkhalter et al. [3] concluded that severe neurologic problems early after transplantation are multifactorial and cannot be ascribed solely to tacrolimus toxicity. In our series, patients switched to CyA showed rapid recovery from neurological adverse reactions. Although tacrolimus-related adverse reactions have been described well, it is not clear our patients' reactions were completely attributable to this drug; organic mental syndrome or other metabolic derangements, for example, may also have played a part in the development of their neurological problems.

IDDM was the second most common adverse reaction in our study. Interestingly, although 17 patients had IDDM requiring conversion, only 5 patients (29.3%) were converted to CyA early after liver transplantation. Twelve patients (70.3%) received increasing doses of insulin and were kept on tacrolimus until their diabetes became uncontrollable, at which point they were converted to CyA; among these 12, 5 required late hospitalization for uncontrollable blood sugar levels. Although the tacrolimus dose was reduced between initial observation of blood glucose elevations and conversion in all 17 patients, dose reduction was clearly not an effective management strategy for IDDM in our patients, resulting in considerable morbidity and increased cost. This outcome contrasts with that of Tabasco-Minguillan at al. [22], who observed that patients with tacrolimus-related IDDM became normoglycemic within 18 months of transplantation. In the European literature, results are controversial as well. In a prospective trial by Steinmüller et al., no patient treated with tacrolimus developed IDDM after liver transplantation [21]. In contrast, Margarit et al. reported that diabetes developed in 33% of liver transplant recipients treated with tacrolimus [13]. In our series, all patients with IDDM responded to conversion, and 15 patients with new-onset IDDM became nondiabetic. Based on our experience, whenever liver recipients on tacrolimus develop new-onset IDDM, we now have a low threshold for conversion to CyA.

Eleven patients had GI toxicity, manifested as nausea, loss of appetite, anorexia, weight loss, abdominal pain, or nonobstructive colonic dilatation (Ogilvie's syndrome). All patients improved dramatically with conversion: their appetites increased, and they gained weight. The patient with Ogilvie's syndrome did not respond to tacrolimus dose reduction or other interventions. His symptoms improved immediately after conversion to CyA, however. We believe that tacrolimus-associated GI toxicity is not dose-related. In our experience, 60% of GI toxicities were accompanied by other

adverse reactions, mainly neurotoxicity (data not shown) [14].

Although the rate of conversion was similar in adults and children (18 vs 14%), in our pediatric population the main indications for conversion were cardiomyopathy, development of PTLD, hepatotoxicity, and neurotoxicity. No children had IDDM or nephrotoxicity requiring conversion to CyA. This may reflect a different spectrum of tacrolimus-associated side effects and tacrolimus tolerance in pediatric patients.

Conversion to CyA generally resulted in improvement, with slight differences between the group converted within 30 days after transplantation and the group converted later. Resolution or improvement of symptoms was observed in all patients converted early after transplantation. Late post-transplant conversion resulted in resolution or improvement of symptoms in 90.2% of patients. The persistence of symptoms in 9.8% of these patients can perhaps be explained by cross-toxicity between tacrolimus and CyA, due to their similar mechanisms of action. In particular, this might be true regarding patients with kidney failure [17]. Another explanation would be that an underlying disease was mistakenly attributed to tacrolimus toxicity. This may have been the case in our 2 patients with symptoms attributed to hepatotoxicity. Although the first biopsies obtained from these 2 patients after the onset of their symptoms suggested tacrolimus hepatotoxicity, their symptoms did not improve after conversion, and subsequent biopsies showed recurrent autoimmune hepatitis in one and steatohepatitis in the other. In particular, elderly patients with neurotoxicity may not respond to conversion to CyA-based immunosuppression and therefore present a special management challenge.

Not surprisingly, acute rejection was more common among patients in the early-conversion group. On the other hand, 4 of 29 early-conversion patients (13.8%) developed rejection within 7 days (range, 2–7 days) after conversion, most likely as a result of low tacrolimus blood levels prior to conversion. Nevertheless, the overall rejection rate in our study population was 30%. This low incidence of rejection might be explained by frequent follow-up and timely dose adjustments. Regardless of the reason, conversion to CyA for tacrolimus-related adverse reactions did not carry an increased risk of rejection in this series of patients compared with the incidence of rejection in previously published series [5, 9, 11]. This finding lends weight to the suggestion that early conversion be considered for patients with new-onset IDDM, rather than continuing tacrolimus and subjecting patients to the metabolic derangements and associated morbidity of diabetes.

The overall incidence of tacrolimus toxicity requiring conversion to CyA was 18%. The number of patients converted annually to CyA had increased each year, from 12% in 1994 to 26% in 1997. With increasing experience and better understanding of the tacrolimus toxicity profile, we have developed a lower threshold for converting patients from tacrolimus to CyA. This approach is especially true for neuropsychiatric toxicity and IDDM.

In conclusion, when tacrolimus-induced side effects occur, a systematic approach to the problem (i.e., dose reduction, close monitoring, and timely conversion) is necessary. In patients with tacrolimus-induced toxicity unresponsive to dose reduction, conversion to CyA is effective and safe, with no increased risk of rejection and with excellent long-term outcome.

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