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ORIGINAL ARTICLE

Open prospective multicenter study of conversion to tacrolimus therapy in renal transplant patients experiencing ciclosporin-related side-effects

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Summary

The hyperlipidemic and hypertensive effects of ciclosporin constitute a cardiovascular risk. Cosmetic side-effects are known to reduce patients' quality of life. This was a 6-month, open, prospective, multicentre study in 296 adult kidney transplant patients to evaluate the conversion from ciclosporin to a tacrolimus-based regimen. Primary indications for conversion were hyperlipidemia ($n = 77$), hypertension ($n = 72$), hypertrichosis ($n = 32$) and gingival hyperplasia ($n = 115$). At month 6, hyperlipidemia and hypertension were at least moderately improved in 59.1% and 63.5% of patients, and strongly or completely resolved in 29% and 25%. Gingival hyperplasia and hypertrichosis were strongly or completely resolved in 73% and 72% of patients. Mean total cholesterol was reduced from 255 to 218 mg/dl. Mean systolic blood pressure (SBP) was reduced from 152.9 to 137.5 mmHg and mean diastolic blood pressure (DBP) from 90.7 to 85.8 mmHg. Ciclosporin-related side-effects resolved or improved after conversion to tacrolimus.

Introduction

Cardiovascular morbidity and mortality among renal transplant patients are substantially greater than in the general population [1] and cardiovascular disorders are responsible for almost half of all deaths with a functioning graft beyond the first year after transplantation [2]. Hyperlipidemia and hypertension increase the risk of major atherosclerotic cardiovascular disease outcomes [3] and are believed to be risk factors for chronic graft nephropathy in renal transplant patients [4]. It is thought that the hyperlipidemic and hypertensive effects of ciclosporin [5] constitute a considerable risk of post-transplant cardiovascular disease and may also reduce long-term

graft survival [6]. Gingival hyperplasia and hirsutism are well-known cosmetic side-effects of ciclosporin therapy [7] that can negatively impact on quality of life and may affect compliance with immunosuppressive therapy, thereby adversely affecting graft survival.

Although many centres still use immunosuppressive regimens based on ciclosporin and corticosteroids, alternative regimens are increasingly being used [8]. It has been suggested that the cardiovascular risk profile of tacrolimus is more favourable than that of ciclosporin as it has less propensity to cause hyperlipidemia and hypertension [9–11]. There have been single centre reports that hyperlipidemic or hypertensive patients, or those suffering from gingival hyperplasia or hypertrichosis associated with ciclosporin use, can be switched to tacrolimus with excellent results [7,12–21]. The objective of this prospective, large-scale, multicentre study of adult primary kidney transplant patients was to evaluate the efficacy and safety of conversion from a ciclosporin-based to a tacrolimus-based immunosuppressive regimen because of ciclosporin-related side-effects.

Materials and methods

Patients

The study was conducted in 30 centres in six European countries. Patients were eligible for inclusion if they were over 18 years of age, had undergone renal transplantation at least 6 months prior to the start of the study, and had received ciclosporin-based immunosuppressive therapy since transplantation. The prescribed dose of ciclosporin had to have been stable for 4 weeks prior to inclusion and all patients had to exhibit stable renal function (baseline creatinine ≤3 mg/dl). Eligible patients had to be suffering from at least one of the following ciclosporin-related side-effects: hyperlipidemia (total cholesterol >220 mg/dl despite treatment with at least one lipid-lowering drug), arterial hypertension (systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg despite treatment with at least one antihypertensive drug), or hypertrichosis or gingival hyperplasia severe enough to require treatment.

Exclusion criteria included: pregnancy/lactation or risk of pregnancy, allergy or intolerance to study drug or structurally related compounds, ongoing systemic immunosuppressive therapy other than for kidney transplantation, known malignant nephrosclerosis, HIV infection, or significant liver disease. Patients were also excluded if they were participating in another clinical trial, taking an investigational drug or had received solid organ grafts other than a kidney.

The study protocol was approved by the ethics committees of each participating centre and was conducted in accordance with the principles of the Declaration of Helsinki. All patients gave written informed consent before inclusion in the study.

Study design

Patients who met the eligibility criteria were included into this open-label, noncomparative study in chronological order following screening on day 0 (baseline) and were followed up for 6 months with a total of four scheduled clinic visits. Demographic characteristics were noted at baseline; patients underwent physical examination, and routine laboratory tests (haematology, biochemistry, renal function, hepatic function, urine protein and lipids) at baseline and weeks 4, 8 and 24. Laboratory parameters were to be taken at the same time of day. Blood pressure was measured in a standardized fashion using equipment that met certification criteria. Patients were to be seated in a standardized manner and had to rest for 5 min before measurements. Three readings separated by 2 min were taken and the average of the three measurements was taken as end-point. The investigators rated the patients' clinical status at baseline and each subsequent visit (the primary study end-point). Patients' ratings of suffering were recorded for hypertrichosis or gingival hyperplasia. Patients converted to tacrolimus because of hypertrichosis were also assessed using the Ferriman-Gallwey index, a grading system (range 0–4) for degree of hypertrichosis for 11 sites of the body (maximum severity score 44). Throughout the study, rejection episodes, serum creatinine levels, adverse events, use of concomitant medication, tacrolimus dose and trough levels (by IMx analysis), ciclosporin wash-out levels (until <50 ng/ml), and the need for dialysis or hospitalization were documented.

Reasons for premature termination of the study included death, graft loss, adverse events, pregnancy, discontinuation of study drug for >14 days, use of prohibited medication, or standard reasons such as protocol deviation or noncompliance.

Study treatments

Conversion from ciclosporin- to tacrolimus-based immunosuppression was performed according to a protocol-driven procedure. The initial dose of tacrolimus (Prograf, Fujisawa GmbH, Munich, Germany) was 0.1 mg/kg/day, divided into two doses, administered twice per day. Tacrolimus was started 12 h after patients received their last dose of ciclosporin. Subsequent doses of tacrolimus were adjusted to achieve whole blood trough levels of 5–15 ng/ml (target 10 ng/ml) by the end of month 1 and 4–10 ng/ml (target 7 ng/ml) by week 24. Concomitant

immunosuppressive therapy was to be maintained after conversion. Patients who received lipid-lowering or antihypertensive drugs within the 14 days prior to conversion to tacrolimus were to continue receiving them at the same dose until study completion. Lipid-lowering and antihypertensive drugs could not be initiated during the study in patients who were not receiving them prior to enrolment.

End-points and statistical analysis

The primary efficacy end-point was the investigator's descriptive rating (completely, strongly, moderately, barely, not at all) of improvement or resolution of the primary indication for conversion to tacrolimus (hyperlipidemia, hypertension, hypertrichosis or gingival hyperplasia) at week 24 compared with baseline. Statistical analyses were performed for the subset of study completers as well as for the total study cohort, using the last observation carried forward (LOCF) procedure for patients who withdrew from the study or had no final visit data. As the results for study completers and for the total study cohort were similar, only the results for study completers are presented in the following.

Secondary efficacy end-points varied according to the reason for conversion to tacrolimus. These were: a change in total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and LDL/HDL ratio and use of lipid-lowering agents in patients converted because of hyperlipidemia; a change in systolic and diastolic blood pressure and use of antihypertensive drugs in patients converted because of hypertension; patients' rating of suffering from hypertrichosis (Ferriman-Gallwey index); gingival hyperplasia in those converted because of adverse cosmetic effects.

Individual differences in blood lipid levels and blood pressure between baseline and week 24 were analysed using Wilcoxon signed rank test (paired analysis). However, 'significance' is meant in an exploratory manner only, as a statistical hypothesis was not prespecified.

Safety parameters included the incidence of adverse events, graft survival, acute rejection, the need for dialysis, and changes in renal function and laboratory parameters. Patients were monitored for the occurrence of adverse events throughout the study and each adverse event was assessed for severity and possible relationship to treatment. Spontaneously reported adverse events were coded using a modified Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) dictionary for statistical analysis. Serious adverse events were to be reported within 24 h and all patients who withdrew from the study were followed-up for serious adverse events for 28 days.

As this was a noncomparative study, no formal sample size calculation was performed. The planned number of 200 patients with a minimum of 40 patients per indication was considered to be sufficient to gain greater insight into the safety and efficacy of conversion from a ciclosporin-based to a tacrolimus-based immunosuppressive regimen. Patient and graft survival analyses were based on the full analysis set which included all enrolled patients who received at least one dose of tacrolimus. Efficacy and safety parameters were analysed for study completers to evaluate the effect of the switch in immunosuppression in stable transplant recipients.

Results

Patient disposition and demographic characteristics

A total of 301 patients were enrolled in the study. Five patients did not receive any study drug which resulted in 296 patients being included in the full analysis set. The primary indications for conversion from ciclosporin to tacrolimus were hyperlipidemia ($n = 77$), arterial hypertension ($n = 72$), hypertrichosis ($n = 32$) and gingival hyperplasia ($n = 115$). Some patients experienced more than one of these conditions (Table 1). Overall, there were more males than females in the study (60% vs. 40%), and nearly all of the patients were Caucasian. The groups were balanced with respect to patient demography, except for the group converted for hypertrichosis who were predominantly female and had a lower mean age (Table 1). The mean time from transplantation was 5.4 years (range 0.5–22.9 years) and the majority of patients (91%) were primary kidney transplant recipients.

The most common adjunctive immunosuppressive medications were corticosteroids (81%), azathioprine (41.6%), and mycophenolate mofetil (25%). Overall, 52.0% received lipid-lowering therapy during the study (primarily atorvastatin, fluvastatin and simvastatin). All except two patients converted to tacrolimus because of hyperlipidemia required lipid-lowering agents at some time during the study as did more than 30% of patients in each of the other three groups. Antihypertensive agents were required by a total of 90.2% of the total cohort and 35.8% received diuretics. All patients in the group converted because of hypertension received antihypertensive therapy. The most commonly used antihypertensive medications (excluding diuretics) were amlodipine, metoprolol and atenolol, furosemide was the most commonly used diuretic.

Investigators' rating of clinical status at week 24

Overall clinical status improved over time. The clinical status was rated as 'completely' (16.4%), 'strongly'

Table 1. Patient disposition and demographic characteristics at baseline.

	Primary reason for conversion				
	Hyperlipidemia	Arterial hypertension	Hypertrichosis	Gingival hyperplasia	Total
Patients enrolled (*n*)	78	75	32	116	301
Full analysis set (*n*)	77	72	32	115	296*
Completed [*n* (%)]†	66 (85.7)	63 (87.5)	32 (100.0)	102 (88.7)	263 (88.9)
Withdrawn [*n* (%)]†	11 (14.3)	9 (12.5)	0 (0.0)	13 (11.3)	33 (11.1)‡
Mean age ± SD (years)†	50.7 ± 10.7	49.1 ± 13.0	43.2 ± 12.6	46.1 ± 12.7	47.7 ± 12.5
Gender [male/female (%)]†	59.7/40.3	73.6/26.4	18.8/81.3	63.5/36.5	60.1/39.9

*Five patients received no study drug.
†All enrolled patients who received at least one dose of tacrolimus.
‡Withdrawn because of adverse events ($n = 22$), graft loss ($n = 1$), lost to follow-up ($n = 1$), protocol deviation ($n = 5$), withdrew consent ($n = 4$).

(34.0%) or 'moderately' (26.0%) improved at week 24 (Fig. 1). The degree of improvement in clinical status differed between the four patient groups.

Hyperlipidemia

In patients who were converted to tacrolimus because of hyperlipidemia associated with ciclosporin therapy, clinical status at week 24 was rated as being at least moderately improved in 59.1%, with a total of 28.8% of patients having strong improvement or complete resolution of hyperlipidemia (Fig. 1). Mean (±SD) total cholesterol was reduced by 15% during the study; 255 (±55) mg/dl at baseline to 218 (±46) mg/dl at week 24.

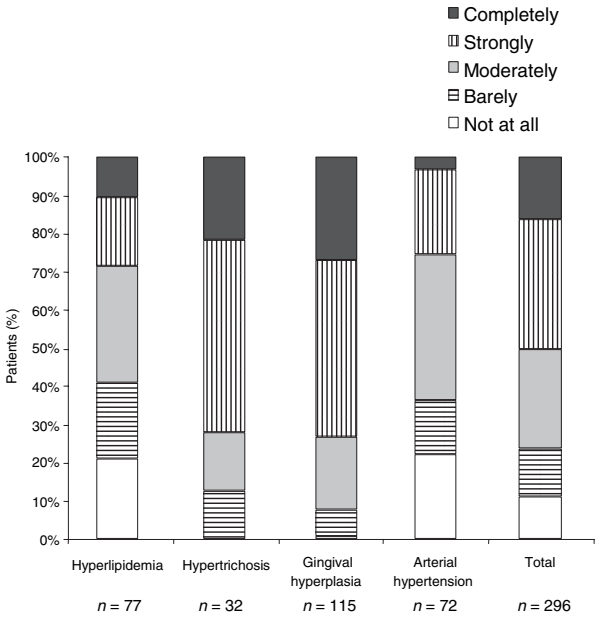

Figure 1 Investigators' ratings of clinical status at week 24 – resolution or improvement of the primary indication for conversion compared with baseline ($n = 296$).

Mean LDL-cholesterol declined by 13%, from 138 (±45) to 120 (±39) mg/dl, while mean HDL-cholesterol remained constant throughout the study (Fig. 2). Mean triglyceride levels were reduced from 324 (245) to 252 (±182) mg/dl while the LDL/HDL ratio improved from 2.9 to 2.5.

The mean change in total cholesterol from baseline (paired analysis) was −0.95 (SD 1.20) mmol/L at week 24 ($P < 0.0001$, Wilcoxon signed rank test); the mean change in LDL-cholesterol was −0.34 (SD 0.93) mmol/L ($P = 0.0259$, Wilcoxon signed rank test); the mean change in triglycerides was −0.80 (SD 1.63) mmol/L ($P < 0.0001$, Wilcoxon signed rank test). When calculated for the total study cohort, the mean changes in these parameters were also highly significant ($P < 0.0001$, Wilcoxon signed rank tests for the changes in total cholesterol, LDL-cholesterol and triglycerides).

Patients with high cholesterol levels at baseline benefited most from conversion to tacrolimus. The proportion

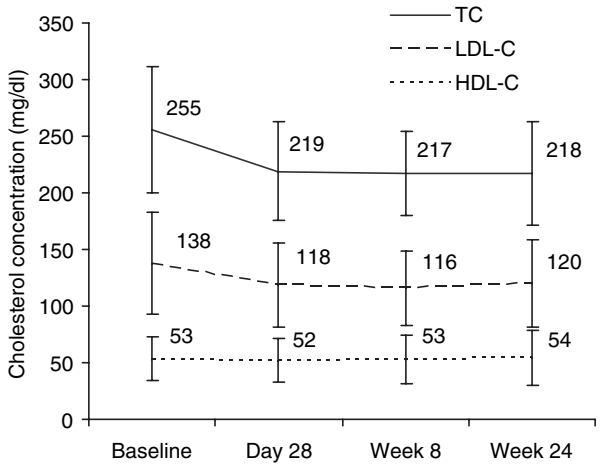

Figure 2 Changes (mean ± SD) in total, LDL- and HDL-cholesterol following switch from ciclosporin to tacrolimus therapy ($n = 77$).

of patients with high (>180 mg/dl) and very high (>250 mg/dl) total cholesterol at baseline was reduced from 96.1% and 35.0% to 72.7% and 14.0% at week 24 in those converted for hyperlipidemia. In the total study cohort, the proportion of patients with high values was reduced from 84.8% at baseline to 61.5% at week 24, the proportion of patients with very high values was reduced from 31.1% to 13.9% during the study.

The improvement in lipid parameters was reflected by a reduced need for lipid-lowering agents during the study. Of the patients who were converted to tacrolimus because of hyperlipidemia 96% received a lipid-lowering drug before the switch compared with 92% at study end (one lipid-lowering medication per patient). The dose of lipid-lowering medication was reduced by an average of 18% during the study.

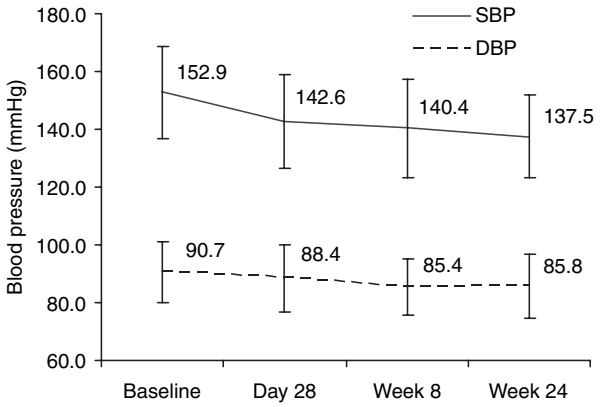

Figure 3 Changes (mean ± SD) in systolic (SBP) and diastolic blood pressure (DBP) following switch from ciclosporin to tacrolimus therapy ($n = 72$).

Hypertension

In the patients who were converted to tacrolimus because of hypertension, clinical status at week 24 was rated by the investigator as having improved at least moderately in 63.5%, with 25.4% of patients rated as 'strongly' or 'completely' resolved. Mean SBP was reduced from 152.9 (±16) mmHg at baseline to 137.5 (±14) mmHg at week 24 and mean DBP from 90.7 (±11) to 85.8 (±11) mmHg (Fig. 3). For patients with primary indication hypertension, mean change in SBP from baseline (paired analysis) was −15.8 (SD 19.32) mmHg ($P < 0.001$, Wilcoxon signed rank test); mean change in diastolic blood pressure was −5.17 (SD 13.05) mmHg ($P = 0.0015$, Wilcoxon signed rank test).

All of these patients received antihypertensive medication at study completion, and the mean number of different antihypertensive drugs remained unchanged (2.2 different antihypertensive medications per patient). However, compared with baseline the doses of antihypertensive medication were reduced by an average of 23% by the end of the study. The proportion of patients with high blood pressure (SBP ≥140 mmHg or DBP ≥90 mmHg) decreased from 96% to 58%. The number of patients in the total study cohort with BP ≥140/90 mmHg was reduced from 184 (62.2%) at baseline to 124 (41.9%) at week 24.

Calculated for the total study cohort, mean changes in systolic and diastolic blood pressure were highly significant ($P < 0.0001$, Wilcoxon signed rank test, for both parameters).

Cosmetic side-effects of ciclosporin

The clinical status of the patients converted for gingival hyperplasia or hypertrichosis improved considerably during the study: according to the investigators' rating symptoms had 'strongly' (73%) or 'completely' (72%) resolved at week 24.

In the hypertrichosis group, mean Ferriman-Gallwey index scores were reduced by 55.5% from 20.9 (±10.0) at baseline to 9.3 (±8.5) at week 24. According to the patients' rating, the percentages of patients who suffered 'strongly' or 'very strongly' from hypertrichosis or gingival hyperplasia were reduced from 68.8% to 3.1% and from 82.7% to 8.0%, respectively, by week 24.

Safety

Conversion to tacrolimus was well tolerated. Only one patient experienced a mild (Banff I) biopsy-confirmed acute rejection on day 176 after conversion. The episode resolved spontaneously without rejection therapy. One patient was diagnosed with chronic rejection on day 107 after the conversion, approximately 5 years after receiving the graft.

No patient died during the study. A total of three patients experienced graft loss, one patient during study and two patients after withdrawal. These patients had received their graft between 4.5 and 16 years before entering the study. Two of these patients were converted to tacrolimus because of hypertension, one patient because of gum hyperplasia. Their serum creatinine had already been high at baseline with values of 213.5, 221.2 and 335.5 μmol/l. Kidney function worsened in these three patients and dialysis was resumed.

The slight decrease of the median serum creatinine level from 135.2 μmol/l at baseline to 132.8 μmol/l at week 24 showed that renal function was stable in the overall study cohort. Serum creatinine clearance median values for the total study cohort improved from 55.80 ml/min at baseline to 57.50 ml/min at week 24.

hyperlipidemia or hypertension remained on lipid-lowering or antihypertensive therapy at the end of the study, symptoms were better controlled than while receiving ciclosporin-based treatment. Furthermore, the beneficial effects of tacrolimus therapy on cardiovascular risk were also observed in patients who were switched from ciclosporin because of cosmetic side-effects.

The reductions in lipids on conversion to tacrolimus seen in this study were consistent with the results of previous studies. These have included a randomized, prospective, multicenter study in the USA in 53 hyperlipidemic kidney transplant patients in which patients who converted to tacrolimus had reductions in total cholesterol, LDL-cholesterol and apolipoprotein B of 16%, 25% and 23%, respectively, while lipid levels remained elevated in ciclosporin-treated patients [14]. Similarly, in a European study, in which 47 kidney graft recipients were converted from ciclosporin to tacrolimus because of worsening lipid metabolism, significant reductions in total cholesterol, LDL cholesterol and triglycerides were evident after 6 and 24 months of follow-up [17]. A 24-h blood pressure monitoring study from the Netherlands which demonstrated that conversion from ciclosporin to tacrolimus produced significant reductions in mean daytime and night-time blood pressures [19]. Moreover, the study by Baid-Agrawal *et al.* [21], with a design similar to the present study but comprising fewer patients, reported a significant improvement of the cardiovascular risk profile after conversion to tacrolimus without any apparent adverse events.

A recently published comparative long-term follow-up of stable renal transplant patients after conversion from ciclosporin to tacrolimus demonstrated that the beneficial effects with respect to cardiovascular risk profile and perceived side-effects are sustained after 2 years [26]. Graft function remained stable after the switch to tacrolimus as opposed to a deterioration in patients who continued ciclosporin therapy. This finding is probably related to the reduction of hyperlipidemia and hypertension, as both are factors that contribute to chronic allograft nephropathy [27–29] but may also hint towards tacrolimus being less nephrotoxic than ciclosporin.

Finally, the clinical status of the patients converted for gingival hyperplasia or hypertrichosis was considerably improved during this study. These findings are supported by those of other studies in which rapid improvements after conversion to tacrolimus were shown in ciclosporin-treated kidney transplant patients with symptoms of gingival hyperplasia and hypertrichosis [7,18].

Overall, safety parameters remained stable following conversion to tacrolimus-based therapy in this study and the occurrence of adverse events was as expected in patients on immunosuppressive therapy. Indeed, many reported adverse events appeared to be related to the patients' original reasons for conversion to tacrolimus. For example, the incidence of hypertension was higher in the group converted because of uncontrolled hypertension on ciclosporin therapy and, as hair loss would be expected with improvement in symptoms of hypertrichosis, it was not surprising that the reported frequency of alopecia was highest in the group converted because of hypertrichosis. In general, the starting dose of tacrolimus 0.1 mg/kg utilized in the study was deemed to be appropriate, but it is recommended that subsequent reductions in tacrolimus dose should be assessed on an individual basis.

The authors admit that the study results are limited to some extend by the lack of a control group. However, the patients who were included into this study had been suffering from unpleasant and harmful side-effects of ciclosporin treatment and it would have been considered unethical to continue ciclosporin in a control arm just for study design reasons.

In conclusion, conversion from ciclosporin- to tacrolimus-based immunosuppressive therapy was both effective and well tolerated in this population of stable kidney transplant patients. Reductions in blood pressure and lipid levels contribute to improvements in cardiovascular risk and reversal of ciclosporin-related cosmetic side-effects may translate into improved treatment compliance.

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Appendix

The European Switch to Tacrolimus Study Group: W. Arns (Cologne, Germany); L. Baeckman (Göteborg, Sweden); G. Cannella (Genova, Italy); C. Casciani (Rome, Italy); N. De Napoli (Cosenza, Italy); K. Lopau (Würzburg, Germany); H. Kachel (Frankfurt, Germany); V. Kliem (Hann Münden, Germany); H. Köhler (Homburg, Germany); F. Leone (Catania, Italy); L. Lombardi (Catanzaro, Italy); Y. Martin (Geneve, Switzerland); L. Rump (Freiburg, Germany); R. Schneidenbach (Würzburg, Germany); D. Scholz (Hamburg, Germany); R. Schwarz (Leipzig, Germany); H. Stummvoll (Linz, Austria); G. Tyden (Stockholm, Sweden); M. Zeier (Heidelberg, Germany); O. Wolfram (Halle, Germany); C. Zoccali (Reggio di Calabria, Italy).

Table 2. Adverse events occurring in ≥5% of patients and overall summary of adverse events.

	Primary reason for conversion [*n* (%)]				
	Hyperlipidemia ($n = 77$)	Arterial hypertension ($n = 72$)	Hypertrichosis ($n = 32$)	Gingival hyperplasia ($n = 115$)	Total ($n = 296$)
Most frequently reported events					
Hypertension	10 (13.0)	19 (26.4)	4 (12.5)	10 (8.7)	43 (14.5)
Creatinine increased	12 (15.6)	9 (12.5)	3 (9.4)	12 (10.4)	36 (12.2)
Diarrhoea	6 (7.8)	6 (8.3)	1 (3.1)	12 (10.4)	25 (8.4)
Urinary tract infection	10 (13.0)	4 (5.6)	4 (12.5)	6 (5.2)	24 (8.1)
Alopecia	4 (5.2)	5 (6.9)	7 (21.9)	5 (4.3)	21 (7.1)
Flu syndrome	5 (6.5)	2 (2.8)	3 (9.4)	11 (9.6)	21 (7.1)
Tremor	6 (7.8)	2 (2.8)	6 (18.8)	4 (3.5)	18 (6.1)
Pruritus	5 (6.5)	5 (6.9)	1 (3.1)	5 (4.3)	16 (5.4)
Anaemia	3 (3.9)	3 (4.2)	3 (9.4)	6 (5.2)	15 (5.1)
Headache	4 (5.2)	4 (5.6)	1 (3.1)	6 (5.2)	15 (5.1)
Overall adverse events	60 (77.9)	50 (69.4)	21 (65.6)	74 (64.3)	205 (69.3)
Serious adverse events	12 (15.6)	10 (13.9	3 (9.4)	12 (10.4)	37 (12.5)
Withdrawn because of adverse events	7 (9.1)	5 (6.9)	0 (0.0)	10 (8.7)	22 (7.4)

Most patients (69.3%) experienced an adverse event during the study, frequencies were similar in all groups (Table 2); 51.0% were judged as being causally related to tacrolimus therapy. The most frequently reported adverse events were hypertension and increased creatinine. The incidence of serious adverse events was 12.5% (5.7% causally related) with no difference between groups (Table 2). Increased creatinine was the only serious adverse event assessed as being causally related to tacrolimus therapy and was reported in a total of four (1.4%) patients.

Pre-existing glucose metabolism disorders were reported in 25 (8.4%) patients at study entry. Of the 271 patients without pre-existing glucose metabolism disorders, one patient (0.4%) received oral antidiabetic treatment during the study. No patient developed new-onset insulin-dependent diabetes mellitus.

Infections occurred in 20.9% of patients. Malignancies were diagnosed in four patients (1.4%): there were two patients with skin carcinomas, one patient with breast carcinoma, and one patient with carcinoma of the mouth. No lymphomas were reported.

Twenty-two patients (7.4%) were withdrawn because of adverse events (Table 2), the majority of which occurred during the first 4 weeks of the study. The main adverse events leading to withdrawal were neurological adverse events (headache, vertigo, agitation, tremor, abnormal vision, myasthenia) followed by dermatologic and nephrological adverse events.

Discussion

Hyperlipidemia and hypertension are important nonimmunologic determinants of graft survival in kidney transplant patients. Hypercholesterolemia and hypertriglyceridemia have been shown to act synergistically with immune reactions in chronic rejection models [22]. Furthermore, hypertension is associated with a poorer outcome and a more rapid decline in graft function, while a reduction of blood pressure improves graft survival and inhibits the glomerular and vascular lesions of chronic rejection [23]. Thus, any intervention that reduces hyperlipidemia and arterial hypertension as risk factors for cardiovascular disease and chronic graft rejection may be beneficial for the patient.

Postrenal transplantation, approximately 67–90% of patients treated with ciclosporin can be expected to develop hypertension, in contrast with about 45–55% prior to the introduction of ciclosporin [6]. In addition, 3-year data from a multicenter study in the USA have indicated that, following cadaveric renal transplantation, approximately 39% of ciclosporin-treated patients required lipid-lowering medication (versus approximately 14% of tacrolimus-treated patients) [24]. Similarly, the 1-year results of a European multicenter study have indicated that approximately 30% of ciclosporin-treated patients had total cholesterol concentrations >240 mg/dl (in contrast with approximately 10% of tacrolimus-treated patients) [25].

This study has demonstrated that cardiovascular risk factors can be substantially reduced in renal transplant patients with ciclosporin-related side-effects who are switched to tacrolimus-based immunosuppressive therapy. The improvement of symptoms started in the first weeks after the conversion and a clear improvement was seen after 6 months of tacrolimus treatment. Although the majority of patients who were converted because of

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