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ADIS DRUG EVALUATION

Tacrolimus Prolonged Release (Envarsus®): A Review of Its Use in Kidney and Liver Transplant Recipients

Karly P. Garnock-Jones

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Abstract Tacrolimus prolonged release (Envarsus®; henceforth referred to as tacrolimus PR) is a new, once-daily, prolonged-release tacrolimus formulation, utilizing a drug delivery technology designed to enhance the bioavailability of drugs with low water solubility by creating a solid solution of the drug. This article reviews the pharmacological properties of tacrolimus PR and its clinical efficacy and tolerability in adult kidney and liver transplant recipients. In phase III trials, tacrolimus PR was noninferior to tacrolimus immediate release (IR; twice daily) in both de novo and stable, previously treated kidney transplant recipients, and had a similar tolerability profile. Preliminary efficacy data from phase II trials in de novo and stable, previously treated liver transplant recipients imply that tacrolimus PR is effective in these patient groups; however, more data would be of interest. Pharmacokinetic analyses demonstrated that tacrolimus PR is associated with a higher bioavailability, reduced peak-trough concentration fluctuation ratio, lower mean values for percentage degree of fluctuation and percentage degree of swing, and a longer time to maximum concentration than tacrolimus IR. Tacrolimus PR is a promising addition to the treatment options available for kidney and liver transplant recipients.

Tacrolimus prolonged release (Envarsus®) in kidney and liver transplant recipients: a summary

Higher bioavailability than other tacrolimus formulations
Less fluctuation of whole-blood tacrolimus concentrations than other tacrolimus formulations
Lower dosage required for similar systemic tacrolimus exposure than with other tacrolimus formulations
Noninferior to tacrolimus immediate release (IR) in de novo and stable, previously treated kidney transplant recipients
Data support its use in de novo and stable, previously treated liver transplant recipients
Generally acceptable tolerability profile, similar to that with tacrolimus IR

1 Introduction

Calcineurin inhibitors are an important part of the recommended combination of treatments for the prevention of transplant rejection [1, 2]; tacrolimus is the recommended first-line calcineurin inhibitor for kidney transplants [1, 2] and is the most common drug used in transplant recipients [3]. Initially, tacrolimus was developed as an immediate-release formulation, requiring twice-daily dosing. As life-long immunosuppression is necessary to maintain allograft

The manuscript was reviewed by: ***K. Budde***, Department of Nephrology, Charité Universitätsmedizin Berlin, Berlin, Germany; ***K.L. Hardinger***, Division of Pharmacy Practice & Administration, University of Missouri-Kansas City, Kansas City, MO, USA.

K. P. Garnock-Jones (✉)
Springer, Private Bag 65901, Mairangi Bay 0754, Auckland, New Zealand
e-mail: demail@springer.com

function in transplant recipients, treatment adherence is a vital factor in the design of a treatment regimen; nonadherence has been associated with graft failure [4]. Once-daily dosing of immunosuppressant drugs has been associated with increased adherence compared with twice-daily administration, in renal transplant recipients [5].

With this in mind, an initial prolonged-release formulation of tacrolimus (Advagraf®) was developed, with the aim of improving adherence to treatment by reducing the dosage schedule of tacrolimus to once- instead of twice-daily [3]. Certain aspects of treatment adherence were improved with the once-daily formulation [6], and it was associated with noninferior efficacy and a similar tolerability profile to that of tacrolimus immediate release (IR), although systemic tacrolimus exposure was reduced with the prolonged-release formulation [3, 7, 8].

Tacrolimus prolonged release (Envarsus®; henceforth referred to as tacrolimus PR) is a new prolonged-release tacrolimus formulation, utilizing a drug delivery technology designed to enhance the bioavailability of drugs with low water solubility by creating a 'solid solution' of the drug [9]. The drug delivery technology used breaks the drug particles down into the smallest possible units, which are sprayed onto a carrier, forming a granulate, which is then compressed into tablets with a stable dissolution profile and particle size [10]. A smaller drug particle size is associated with a greater drug surface area and thus with greater drug absorption [10]. This article reviews the pharmacological properties of tacrolimus PR and its clinical efficacy and tolerability in adult kidney and liver transplant recipients.

2 Pharmacodynamic Properties

The pharmacodynamic profile of tacrolimus (any formulation) is well established, and has been extensively reviewed elsewhere [11–15]. This section provides a brief overview of the data.

Tacrolimus binds to immunophilin FK506 binding protein 12 (FKBP12), a cytosolic protein responsible for its intracellular accumulation [11–16]. The tacrolimus-FKBP12 complex then specifically and competitively binds to calcineurin, blocking its phosphatase activity [11–16]. The inhibition of calcineurin leads to a calcium-dependent inhibition of the T-lymphocyte signal transduction pathways responsible for the transcription of certain cytokine genes involved in immune response [16]. Cytokines involved in the cell-mediated immune response (produced by T helper-1 lymphocytes) are preferentially suppressed over those involved in the stimulation of the humoral immune response (produced by T helper-2 lymphocytes) [11, 13].

Tacrolimus inhibits cytotoxic lymphocytes; these are largely responsible for graft rejection in allograft recipients [11, 12, 16]. The drug suppresses the activation of T lymphocytes, the T-helper lymphocyte-dependent activation and proliferation of B lymphocytes, and the calcium-dependent proliferation of B lymphocytes, and suppresses lymphokine [e.g. interleukin (IL)-2, IL-3 and interferon-γ] formation and IL-2 receptor expression [11–14, 16].

Tacrolimus does not inhibit the secondary proliferation of activated T lymphocytes in response to IL-2, and it does not affect antigen presentation or mononuclear phagocyte or natural killer cell function [12–15].

A summary of the pharmacodynamic properties associated with tacrolimus is presented in Table 1.

Pharmacodynamic drug interactions (increased nephro- or neurotoxic effects) may occur between tacrolimus and coadministered drugs known to also have these effects [16]. Tacrolimus may be associated with hyperkalaemia (or may exacerbate pre-existing hyperkalaemia); ingestion of high levels of potassium or use of potassium-sparing diuretics should be avoided [16]. The use of live attenuated vaccines with tacrolimus treatment should also be avoided, as immunosuppressants may affect the response to vaccination, making it less effective [16].

Tacrolimus may prolong the QT interval [17]. In a phase III trial in de novo kidney transplant recipients (see Sect. 4.1.1 for study details), tacrolimus [both PR (Envarsus®) and IR] recipients showed no significant changes from baseline in ECG parameters, and there was no evidence of prolongation of the PR interval, QRS complex or QT interval [10].

3 Pharmacokinetic Properties

The prolonged-release formulation of tacrolimus PR (Envarsus®) results in an extended oral absorption profile (counteracting the generally rapid absorption of tacrolimus), with a median time to maximum concentration (C_{max}) in blood of ≈6 h at steady state [16]. Tacrolimus has been shown to be absorbed throughout the gastrointestinal tract in humans [16, 18]; initial disintegration of the formulation occurs in the stomach and/or proximal small bowel within ≈1 h, and complete disintegration in the distal small bowel or colon within ≈9 h [18].

Tacrolimus has a variable absorption, with a mean oral bioavailability of 20–25 % and an individual range in adults of 6–43 % [16]. When tacrolimus PR was administered after a high-fat meal, the oral bioavailability was decreased (extent of absorption by 55 % and plasma C_{max} by 22 %); tacrolimus PR should be taken on an empty stomach [16]. Tacrolimus PR can be taken in the morning or the evening; no significant time-of-treatment differences

Table 1 Overview of important tacrolimus pharmacodynamic properties

Inhibits several immune responses with higher (10- to 100-fold) potency than ciclosporin, in vitro [11–15]
Cell-mediated immune responses suppressed in animal models of transplantation [11, 13, 15]
Lower level of interstitial infiltration by T lymphocytes and monocytes/macrophages than with ciclosporin [11]
Can cause nephrotoxicity [11–15]; however, associated with better renal function (serum creatinine levels and glomerular filtration rates) than ciclosporin with long-term treatment [12]
Diabetogenic effects (e.g. decreased insulin sensitivity and β-cell secretory reserve, impaired β-cell/α-cell axis) [11–14]
Neurological effects (e.g. increased apoptosis in brain capillary epithelial cells) [11, 12]
Mean total and low-density-lipoprotein cholesterol levels lower than with ciclosporin; no treatment differences in high-density-lipoprotein cholesterol or triglyceride levels) [11–14]

in tacrolimus pharmacokinetics were found in healthy volunteers [19]. However, the EU summary of product characteristics recommends that it should be taken in the morning [16].

Tacrolimus PR has an oral bioavailability that is ≈40 % higher than that of tacrolimus IR in kidney transplant recipients [16]. Moreover, tacrolimus PR is associated with a significantly reduced peak-trough fluctuation ratio and a significantly longer time to C_{max} than tacrolimus IR (Table 2), as well as significantly lower mean values for percentage degree of fluctuation and percentage degree of swing (all $p < 0.05$) [9, 16, 20, 21]. Tacrolimus PR was also associated with a significantly ($p < 0.001$) lower C_{max} than tacrolimus IR in stable, previously treated kidney [9] and liver [20] transplant recipients, although the difference was not significant in de novo kidney transplant recipients [22]. Trough concentration (C_{trough}) did not differ between tacrolimus PR and tacrolimus IR in any of these studies (Table 2) [9, 20, 22]. The differences between tacrolimus PR and tacrolimus IR in concentration over time are shown in Fig. 1.

In equal-dosage (2 mg/day) comparisons at steady-state, tacrolimus PR was associated with a significantly reduced peak-trough fluctuation ratio (1.85 vs. 2.59), significantly longer time to C_{max} (8 vs. 2 h), and significantly higher average concentration (5.93 vs. 3.92 ng/mL), C_{max} (8.39 vs. 7.00 ng/mL), C_{trough} (4.66 vs. 2.80 ng/mL) and area under the concentration-time curve (AUC) from time zero to 24 h (142.27 vs. 94.15 ng·h/mL) values than the earlier prolonged-release formulation in healthy volunteers (all $p < 0.05$) [23].

Adult kidney and liver transplant recipients required a total daily dose of tacrolimus PR that was ≈30 % lower than that of tacrolimus IR to achieve similar systemic exposure levels at 7 days, in phase II conversion studies [9, 20].

There is a strong correlation ($r \approx 0.9$; $p < 0.0001$ [9, 22]) between whole-blood C_{trough} and the AUC at steady

Table 2 Pharmacokinetics of tacrolimus prolonged release (Envarsus®) vs. tacrolimus immediate release

Pt population	Treatment (no. of pts)	TDD (mg/day)	AUC_{24} (ng·h/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)	t_{max} (h)	C_{max}/C_{trough} ratio	C_{trough}–AUC_{24} correlation coefficient
De novo KTRs[a] [22]	TAC PR (32)		319.85	27.41	9.18			0.94[b]
	TAC IR (31)		286.69	24.12	10.35			0.96[b]
Stable, previously treated KTRs[c] [9]	TAC PR (47)	5.26*	206.79	12.64***	6.59	6.00***	2.03***	0.91
	TAC IR (47)	7.39	212.12	17.66	6.82	1.82	2.75	0.79
Stable, previously treated LTRs[d] [20]	TAC PR (57)	4.42	185.48	11.80**	5.91	6.00**[e]	2.12**	0.94
	TAC IR (57)	6.10	196.43	16.86	6.40	1.50[e]	2.75	0.90

Data were taken at day 7 from whole-blood samples and are means, unless otherwise specified

AUC_{24} area under the concentration-time curve from time zero to 24 h, *C_{max}* maximum concentration, *C_{trough}* trough concentration, *KTRs* kidney transplant recipients, *LTRs* liver transplant recipients, *pts* patients, *TAC PR* tacrolimus prolonged release, *TAC IR* tacrolimus immediate release, *TDD* total daily dosage, *t_{max}* time to C_{max}

* $p < 0.05$, ** $p < 0.001$, *** $p \leq 0.0001$ vs. comparator formulation

[a] Following transplant, pts were randomized to treatment with TAC PR 0.14 mg/kg/day (0.17 mg/kg/day in Black pts) or TAC IR 0.2 mg/kg/day (divided into two daily doses); subsequent dosage was adjusted to maintain a C_{trough} of 7–20 ng/mL

[b] Day 14

[c] Pts already receiving TAC IR (at a dosage aiming to achieve a C_{trough} of 7–12 ng/mL) were converted to TAC PR using a dose conversion ratio of 0.70 (range 0.66–0.80), and maintained at a dosage aiming to achieve a C_{trough} of 5–15 ng/mL

[d] See Sect. 4.2 for treatment details

[e] Median

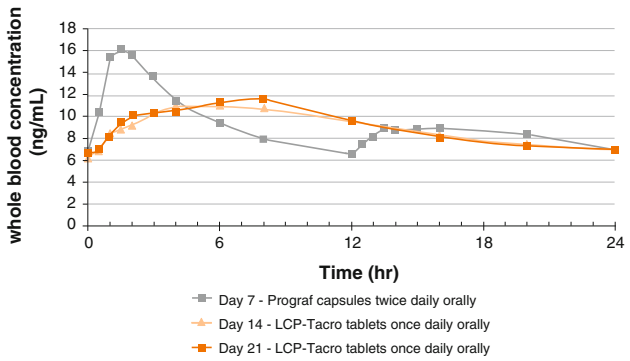

Fig. 1 Mean whole-blood tacrolimus concentration vs. time curve for tacrolimus prolonged release (LCP-Tacro) at 7 and 14 days and tacrolimus immediate release (Prograf®) at 7 days in a phase II conversion study in stable, previously treated kidney transplant recipients [9]. Patients received 7 days' treatment with tacrolimus immediate release before crossing over to tacrolimus prolonged release for 14 days. Dosage details are shown in Table 2. Reproduced from Gaber et al. [9], with permission

state with tacrolimus PR (Table 2); thus, whole-blood C_{trough} monitoring can provide an estimate of systemic exposure to the drug [16].

Tacrolimus has a biphasic distribution when administered as an intravenous infusion in the clinical setting [16]. Systemically, tacrolimus has a ≈20:1 distribution ratio of whole-blood:plasma concentrations, as it binds strongly to erythrocytes. Plasma protein binding of tacrolimus is >98.8 % (mainly to serum albumin and α-1-acid glycoprotein) [16].

Tacrolimus is extensively distributed. The steady-state volume of distribution of tacrolimus is ≈1,300 L based on plasma concentrations and 47.6 L based on whole-blood concentrations, in healthy volunteers [16]. Tacrolimus crosses the placenta and is excreted in breast milk [16].

Metabolism of tacrolimus occurs in the liver [by cytochrome P450 (CYP)3A4] and in the intestinal wall [16]. Several metabolites have been identified. One has been shown (in vitro) to have immunosuppressive activity to a similar degree to that with tacrolimus; all others have weak or no immunosuppressive activity. However, tacrolimus metabolites do not contribute to its pharmacological activity in patients, as only one of the metabolites is present in systemic circulation (an inactive one), and only at low concentrations [16].

As a low-clearance drug, tacrolimus has an average total body clearance of 2.25 L/h, estimated from whole blood concentrations from healthy volunteers; however, the average total body clearance in adult kidney transplant recipients was 6.7 L/h [16]. This higher clearance rate following transplantation is thought to be associated with increased metabolism (induced by corticosteroids), or with low haematocrit and protein levels (resulting in an increase in the unbound fraction of tacrolimus). Tacrolimus has a long, variable half-life; the mean half-life in whole blood is approximately 30 h in healthy volunteers [16].

Following intravenous and oral administration of ^{14}C-labelled tacrolimus, most radioactivity was eliminated in the faeces; the urine contained only ≈2 % of the radioactivity [16]. Bile is the principal route of elimination; tacrolimus is almost completely metabolized before elimination, as shown by <1 % of unchanged tacrolimus being present in the urine or faeces.

3.1 Potential Drug Interactions

As tacrolimus is metabolized by CYP3A4, both systemically and in the intestinal wall, concomitant use of drugs known to inhibit or induce CYP3A4 activity may affect the metabolism of tacrolimus [16].

Substances known to increase tacrolimus concentrations (mainly as a result of increased oral bioavailability due to inhibited CYP3A4-associated gastrointestinal metabolism) include antifungal agents, erythromycin, HIV protease inhibitors and hepatitis C virus protease inhibitors, among others [16].

Substances known to decrease tacrolimus blood concentrations via the induction of CYP3A4 activity include rifampicin, phenytoin, phenobarbital, hypericum (St John's wort), and maintenance dosages of corticosteroids [16].

High-dose prednisolone or methylprednisolone, when administered for the treatment of acute kidney rejection, have the potential for interaction with tacrolimus, leading to increased or decreased tacrolimus blood concentrations [16].

As tacrolimus is extensively bound to plasma proteins, there is a potential for interactions leading to increased tacrolimus blood concentrations with other active substances with a high affinity for plasma proteins, such as NSAIDs, oral anticoagulants or oral antidiabetics agents [16]. Coadministration with prokinetic agents (e.g. metoclopramide, cisapride), cimetidine and magnesium-aluminium-hydroxide also all have the potential to result in increased tacrolimus blood concentrations, as does grapefruit juice.

Tacrolimus is also a CYP3A4 inhibitor itself; as such, it may affect the metabolism of substances metabolized by this enzyme [16]. For example, the half-life of ciclosporin is extended when these drugs are administered concomitantly, and tacrolimus is associated with an increased phenytoin concentration when coadministered with this drug. Tacrolimus may also reduce the clearance of steroid-based contraceptives, leading to increased hormone

exposure, and may potentially decrease the clearance and increase the half-life of pentobarbital and antipyrine.

3.2 Special Patient Populations

Black patients may require higher doses of tacrolimus PR than non-Black patients to achieve similar C_{trough} values [16]. In a phase II pharmacokinetic study using dosages targeted to achieve a C_{trough} of 5–15 ng/mL, Black patients had a significantly higher mean C_{max}, degree of fluctuation and degree of swing (all $p < 0.001$) than non-Black patients; however, this difference was consistently less than that observed with tacrolimus IR [9]. Black patients are statistically more likely than non-Black patients to have the CYP3A5 genetic polymorphism, resulting in increased clearance and lower oral bioavailability of tacrolimus [9].

Dosage reduction may be required in patients with severe hepatic impairment, as metabolism occurs in the liver [16]. The pharmacokinetics of tacrolimus are unaffected by renal function. No data are available indicating any need for dosage adjustments in elderly patients [16].

4 Therapeutic Efficacy

4.1 Kidney Transplants

Data from two randomized, double-blind [10] or open-label [24], tacrolimus IR-controlled, multicentre, noninferiority, phase III trials are available [10, 24]. Data from a phase II trial indicated that tacrolimus PR (Envarsus®) was effective in de novo kidney transplant recipients [treatment failure rate of 6.3 % in 32 tacrolimus PR and 9.7 % in 31 tacrolimus IR recipients; graft and patient survival rate of 100 % in both groups; dosage adjustments 3.25 vs. 4.90 per patient (first 14 days; $p < 0.01$)] [22, 25]; this trial is not discussed further.

4.1.1 In De Novo Patients

Adult, de novo kidney transplant recipients were randomized to treatment with tacrolimus PR tablets once daily ($n = 268$) or tacrolimus IR capsules twice daily ($n = 275$) (initial total daily doses of 0.17 and 0.10 mg/kg/day, respectively) [10]. Subsequent doses were adjusted (after the initial 48 h) to maintain a tacrolimus C_{trough} of 6–11 ng/mL for the first 30 days and 4–11 ng/mL thereafter. All patients also received concurrent mycophenolate mofetil 2 g/day, basiliximab and corticosteroid treatment.

Exclusion criteria included patients who had received another organ or bone marrow transplant; who had a panel-reactive antibody score >30 %; or who had used sirolimus, everolimus, azathioprine or cyclophosphamide in the past 3 months [10].

The primary endpoint was the treatment failure rate at 12 months; treatment failure was a composite endpoint which comprised the first instance of death, graft failure, centrally read biopsy-proven acute rejection (Banff grade $\geq$ 1A), or lost to follow-up [10]. The noninferiority of tacrolimus PR to tacrolimus IR was shown if the upper bound of the 95 % CI for the treatment difference in treatment failure rate was <10 %.

Most patients (77 %) were White; 5 % were Black [10]. At baseline, the mean age was 46 years. A total of 51 % of kidneys came from deceased donors, 96 % of patients had not received previous transplants, 20 % had pre-transplant diabetes mellitus, and 91 % of patients had panel-reactive antibody scores of <5 %. The mean time from transplant to first dose was 34 h.

The total daily dose was higher among tacrolimus PR than tacrolimus IR recipients for the first 10 days and similar from day 10 to week 3, after which it was lower, with an increasing between-group difference seen over time [10]. Over the study, the cumulative dose of tacrolimus PR was 14 % lower than that of tacrolimus IR; the mean total daily dose at month 12 was 4.09 mg in tacrolimus PR recipients and 5.01 mg in tacrolimus IR recipients.

Following the first study dose, the target tacrolimus C_{trough} was reached by 37 and 19 % of tacrolimus PR and tacrolimus IR recipients, respectively [10]. C_{trough} values were higher among tacrolimus PR than tacrolimus IR recipients for the first 2 weeks, and similar from then through 12 months. At 12 months, the mean tacrolimus C_{trough} was 6.50 ng/mL in both treatment groups. The C_{trough}:dose ratio was significantly ($p \leq 0.02$) higher in tacrolimus PR than in tacrolimus IR recipients at all time points except week 3, reflecting the higher bioavailability of the prolonged-release formulation.

Tacrolimus PR was noninferior to tacrolimus IR with regard to the treatment failure rate at 12 months (primary endpoint) in de novo kidney transplant recipients (Fig. 2) [10]. Moreover, no significant differences were found between treatment groups in the individual components of treatment failure (Fig. 2).

In the first 3 months post-transplant (often a time of heightened risk of rejection), the treatment failure rate was 10 versus 14 % in tacrolimus PR versus tacrolimus IR recipients [10]. The respective rates of death, graft failure and biopsy-proven acute rejection were 0 versus 2 %, 2 versus 3 % and 8 versus 10 % at 3 months.

The treatment groups did not significantly differ with regard to the distribution of time to treatment failure event on a Kaplan-Meier projection, nor were there significant

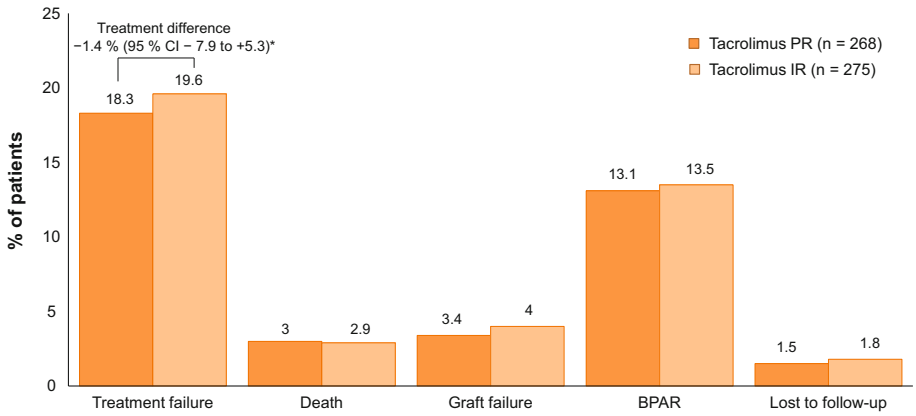

Fig. 2 Treatment failure rate within 12 months (primary endpoint), and the rates of its individual components, for tacrolimus PR vs. tacrolimus IR in de novo kidney transplant recipients [10]. *BPAR* biopsy-proven acute rejection, *PR* prolonged release, *IR* immediate release. * indicates noninferiority criteria were met

differences with regard to time to first episode of biopsy-proven acute rejection [10].

At 12 months, overall survival was 97 % in both tacrolimus PR and tacrolimus IR recipients; graft survival was 97 and 96 %, respectively, and graft and patient survival combined was 94 % in both groups [10].

The incidence of clinically suspected and treated rejection was 14 versus 16 % in tacrolimus PR versus tacrolimus IR recipients, and no significant treatment differences were found in the number of biopsy-proven acute rejection episodes, or in the severity of the first biopsy-proven acute rejection (mild in 11 %, moderate in 3 % and severe in <1 % of patients in both groups) [10].

4.1.1.1 Two-Year Follow-Up A total of 195 tacrolimus PR and 199 tacrolimus IR recipients completed 24 months of follow-up on their assigned treatment [26]. At 24 months, the treatment failure rate was 23.1 versus 27.3 %, respectively, with a treatment difference of −4.14 (95 % CI −11.38 to +3.17), again demonstrating noninferiority.

The incidence of the individual events comprising treatment failure were similar between treatment groups at 24 months: biopsy-proven acute rejection occurred in 17.2 % of tacrolimus PR recipients and 18.2 % of tacrolimus IR recipients, graft failure in 4.1 and 5.5 %, respectively, death in 4.1 and 4.7 %, and lost to follow-up in 1.5 and 2.9 % [26]. Renal function was also similar between treatment groups over the 24-month period.

The total daily tacrolimus dose was ≈25 % lower in tacrolimus PR than in tacrolimus IR recipients in the second year of treatment; C_{trough} values remained similar [26].

4.1.2 In Stable, Previously Treated Patients

The Multicenter Evaluation of LCPT Tablets (MELT) trial compared tacrolimus PR tablets with tacrolimus IR capsules in patients who were stable, adult (≥18 years) recipients of a living- or deceased-donor kidney transplant (received 3 months to 5 years before screening) and who were being treated with a stable dosage of twice-daily tacrolimus IR (C_{trough} of 4–15 ng/mL) [24]. Patients were randomized to transfer to tacrolimus PR once daily at an initial dosage of 0.7 times the total tacrolimus IR dosage (0.85 times in Black patients) ($n = 163$) or to remain on twice-daily tacrolimus IR therapy ($n = 163$). Dosage was adjusted in both groups to a target tacrolimus C_{trough} of 4–15 ng/mL in whole blood.

Exclusion criteria included patients who had received another organ or bone marrow transplant, had been treated with sirolimus or everolimus within the past 3 months, or who were receiving mycophenolate mofetil dosages that had not been stable for ≥4 weeks [24].

The primary endpoint was the efficacy failure rate at 12 months in the modified intent-to-treat population ($n = 162$ in each group); efficacy failure comprised death, graft loss, loss to follow-up or locally read biopsy-proven acute rejection (Banff grade ≥ 1A) [24]. The noninferiority of tacrolimus PR to tacrolimus IR was shown if the upper bound of the 95 % CI for the treatment difference in efficacy failure rate was <9.0 %.

In general, no significant between-group differences in baseline characteristics were found [24]. Most patients (73 %) were White; 21 % were Black. The mean age was 50 years. A total of 13 % of patients had experienced previous rejection for the current graft, 65 % of donated kidneys came from deceased donors, 76 % of patients had more than three human leukocyte antigen mismatches, 64 % of patients had panel-reactive antibody scores of <5 %, and 38 % of patients had pre-transplant diabetes. Tacrolimus PR recipients had a significantly longer time since transplant than tacrolimus IR recipients (25.9 vs. 22.1 months; $p = 0.034$).

Over the 12 months of the study, the mean daily dose of tacrolimus was ≈20 and ≈4 % lower than baseline tacrolimus IR dosage in the tacrolimus PR and the tacrolimus IR group, respectively [24]. The mean daily dose in the tacrolimus PR group was significantly lower than baseline

at all timepoints ($p < 0.0001$); in the tacrolimus IR group it was significantly different from baseline from month 3 onwards ($p < 0.05$–0.0001). At 12 months, the mean daily dosage was 4.7 and 4.9 mg/day, respectively, from baseline (pre-conversion) dosages of 6.1 and 5.3 mg/day.

Mean tacrolimus C_{trough} values were similar between the treatment groups and remained within the target range throughout the study [24]. The mean daily dosage in Black patients was greater than that for non-Black patients, and was similar between treatment groups.

Tacrolimus PR was noninferior to tacrolimus IR with regard to the efficacy failure rate at 12 months (primary endpoint) in stable, previously treated kidney transplant recipients (Fig. 3) [24]. When biopsies were centrally (rather than locally) read, the efficacy failure rate was 1.9 versus 3.7 % in recipients of tacrolimus PR versus tacrolimus IR (treatment difference −1.9 %; 95 % CI −6.5 to +2.3). The centrally read biopsy-proven acute rejection rate was 0.6 versus 2.5 %, respectively.

The efficacy failure rate, graft loss rate, mortality and acute rejection rate were all low and similar between treatment groups at 6 months [24]. As could be expected in an open-label conversion study in maintenance renal transplant recipients, significantly more tacrolimus PR than tacrolimus IR recipients discontinued treatment prematurely within 12 months (12 and 5 %; $p = 0.028$).

At 12 months, patient survival was 98.8 % in the tacrolimus PR group and 99.4 % in the tacrolimus IR group [24]. The death-censored graft survival rate at 12 months was 100 % in both groups.

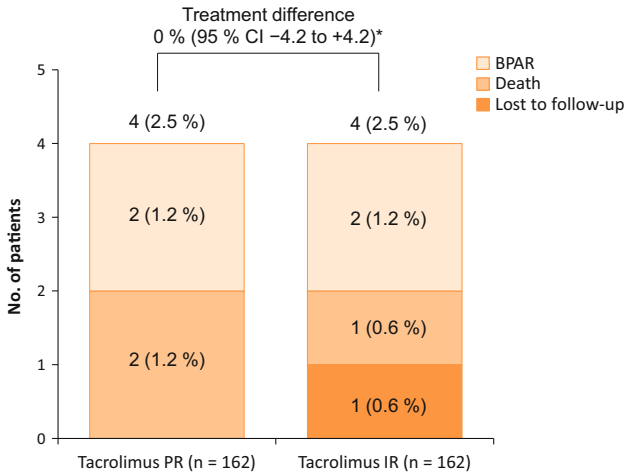

Fig. 3 Efficacy failure rate within 12 months (primary endpoint) for tacrolimus PR vs. tacrolimus IR in stable, previously treated kidney transplant recipients [24]. No patients in either treatment group experienced graft loss, no tacrolimus PR recipients were lost to follow-up. *BPAR* biopsy-proven acute rejection, *PR* prolonged release, *IR* immediate release. * indicates noninferiority criteria were met

4.1.3 Pooled Subgroup Analyses of Phase III Trials

Exploratory, post-hoc, subgroup analyses of pooled data from both phase III trials found that tacrolimus PR was associated with a significantly ($p < 0.05$) lower treatment failure rate than tacrolimus IR in Black patients (treatment difference −13.8 %; 95 % CI −27.2 to −0.3) and patients aged ≥65 years (−13.5 %; 95 % CI −25.3 to −0.8) [27]. Patient numbers were much lower for Black ($n = 93$) than non-Black ($n = 768$) patients and for patients aged ≥65 ($n = 84$) than those aged <65 ($n = 777$) years.

No significant treatment difference was found in any other subgroup investigated (de novo/stable patients, patients aged <65 years, male/female patients, non-Black patients, patients with BMI <30/≥30 kg/m^2, US/non-US patients, patients who were diabetic/non-diabetic at baseline) [27].

4.2 Liver Transplants

Data from two tacrolimus IR-controlled, multicentre, phase II trials in liver transplant recipients are available: one randomized trial in de novo patients [21] and one non-comparative conversion trial in stable, previously treated patients [20]. These trials both focused on pharmacokinetic data; efficacy data are sparse in this patient group.

In de novo liver transplant recipients, patients were randomized to initial treatment with tacrolimus PR 0.07–0.11 mg/kg/day (0.09–0.13 mg/kg/day in Black patients) (once daily) or tacrolimus IR 0.10–0.15 mg/kg/day (divided twice-daily) [21]. Dosages of both drugs were subsequently adjusted to maintain a tacrolimus C_{trough} of 5–20 ng/mL (first 90 days) and 5–15 ng/mL (remaining study period). Efficacy was monitored for 1 year. A total of 6 of 29 tacrolimus PR and 4 of 29 tacrolimus IR recipients had biopsy-proven acute rejection at day 360, and two patients in each group died during the study. Tacrolimus C_{trough} values did not differ significantly between tacrolimus PR and tacrolimus IR recipients, with 24 and 35 % of patients in each treatment group reaching the target C_{trough} range at day 2. Dosage adjustments occurred a mean of 3.9 versus 4.8 times per patient in the first 14 days.

In stable, previously treated patients, recipients of stable dosages of twice-daily tacrolimus IR (tacrolimus C_{trough} of 5–12 ng/mL) continued on tacrolimus IR for 1 week and then were converted to once-daily tacrolimus PR (conversion ratio target of 0.70; range 0.66–0.80), receiving a fixed dosage for 1 week, after which one dosage adjustment was permitted on day 15 [20]. After the initial 3-week study, patients could enter a 50-week extension study, during which they received tacrolimus PR to maintain a recommended tacrolimus C_{trough} of 5–15 ng/mL. No patients

experienced graft loss or died during the initial study or the extension study.

5 Tolerability

Tacrolimus PR (Envarsus®) had a generally acceptable tolerability profile in kidney and liver transplant recipients in clinical trials [10, 20, 21, 24].

In de novo kidney transplant recipients, 97 % of tacrolimus PR and 98 % of tacrolimus IR recipients had at least one adverse event [10]; corresponding proportions in stable, previously treated kidney transplant recipients were 83 and 82 % [24]. Of the 3,128 and 3,214 adverse events in de novo patients receiving tacrolimus PR or tacrolimus IR, 13 and 14 % were considered to be potentially treatment-related [more than half of the patients in both treatment groups (62 and 55 % of patients, respectively) experienced at least one potentially treatment-related adverse event in this study] [10]; corresponding event proportions in stable, previously treated patients were 7 and 6 % of 699 and 571 events, respectively [24]. The mean number of adverse events experienced per patient was 11.7 (both treatment groups) in de novo patients [10]. The most common adverse events in these trials are presented in Fig. 4a and b, and are all commonly known to occur in kidney transplant recipients being treated with immunosuppressant drugs.

A total of 12 % of de novo kidney transplant recipients in both treatment groups withdrew from treatment as a result of at least one adverse event [10]; in stable, previously treated kidney transplant recipients, 8 % of tacrolimus PR and 1 % of tacrolimus IR recipients withdrew from treatment as a result of adverse events (almost all C_{trough} values in these patients were within the target range) [24].

Serious adverse events occurred in 53 % of tacrolimus PR (389 events) and 59 % of tacrolimus IR (415 events) recipients in de novo kidney transplant recipients; the most common serious events included urinary tract infections (9 and 7 %), kidney transplant rejection (5 and 8 %) and complications of transplanted kidney (3 and 7 %; mostly delayed graft function) [10]. A total of 8 patients (3 %) died in each treatment group. No deaths in the tacrolimus PR group were considered related to study treatment; three deaths in the tacrolimus IR group were considered related: two patients with sepsis and one with cardiac failure due to pneumonia.

In kidney transplant recipients who were previously stable on tacrolimus IR, serious adverse events occurred in 22 % of tacrolimus PR (52 events) and 16 % of tacrolimus IR (42 events) recipients [24]. A total of 2.5 % of the serious adverse events in each treatment group were considered to be related to study treatment. No serious adverse events had incidences of ≥5 %; the most common serious adverse event was urinary tract infection (2 vs. 3 %). Two patients (1 %) in the tacrolimus PR group died during the study; neither death was considered related to study treatment.

Among Black stable, previously treated kidney transplant recipients, 89 % of tacrolimus PR and 97 % of tacrolimus IR recipients had at least one adverse event; 29 and 21 % had at least one serious adverse event [24].

As an immunosuppressive agent, tacrolimus increases the risk of infection, and the course of pre-existing infections may be aggravated [16]. In de novo kidney transplant recipients, the incidence of opportunistic infection was 34 % in tacrolimus PR and 31 % in tacrolimus IR recipients (Fig. 4a); cytomegalovirus infection occurred in 12 and 9 % of patients and BK virus infection in 9 and 10 % [10]. In stable, previously treated kidney transplant recipients, opportunistic infections occurred in 6 % of patients in both treatment groups [24].

Recipients of immunosuppressive treatment are also at an increased risk of developing malignancies, in particular Epstein-Barr virus-associated lymphoproliferative disorders [16]. Malignancies developed in 2 % of tacrolimus PR and 1 % of tacrolimus IR recipients in de novo kidney transplant recipients [10]; corresponding incidences were 5 and 6 % in stable, previously treated kidney transplant recipients [24].

In de novo kidney transplant recipients, the incidence of delayed graft function was 7 % in tacrolimus PR and 11 %

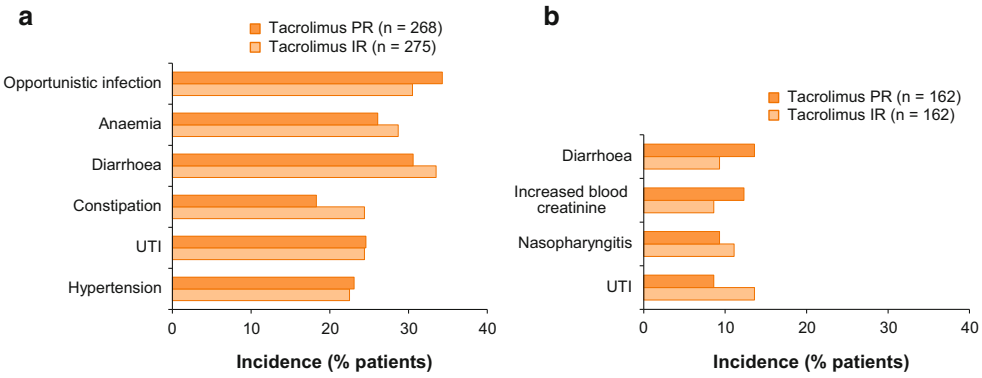

Fig. 4 Tolerability of tacrolimus PR vs. tacrolimus IR in **a** de novo [10] and **b** stable, previously treated [24] kidney transplant recipients. Incidence of adverse events occurring in **a** ≥20 % or **b** ≥10 % of patients in either treatment group. *PR* prolonged release, *IR* immediate release, *UTI* urinary tract infection

in tacrolimus IR recipients [10]. Thus, the higher initial exposure to tacrolimus with tacrolimus PR than with tacrolimus IR was not associated with an increased risk of delayed graft function [28].

New-onset diabetes mellitus (NODM) occurred in 21 and 15 % of at-risk de novo kidney transplant recipients receiving tacrolimus PR and tacrolimus IR, respectively [10]. The change in glycated haemoglobin did not significantly differ between treatment groups at months 3, 6 and 12 [10]. In stable, previously treated kidney transplant recipients, NODM occurred in 8 and 8 % of at-risk patients within 6 months, respectively, and 10 and 11 % at 12 months [24].

Laboratory measures, including estimated glomerular filtration rate, total cholesterol, low-density lipoprotein cholesterol, triglycerides [10, 24] and high-density lipoprotein cholesterol [10], did not significantly differ between treatment groups in either de novo [10] or stable, previously treated [24] kidney transplant recipients.

An exploratory analysis in de novo kidney transplant recipients found that the higher tacrolimus starting dose in the tacrolimus PR than in the tacrolimus IR group was not associated with an increased risk of adverse events [29]. The incidence of adverse events, including serious adverse events, was not significantly different between treatment groups either pre- or post-day 30, nor was that of adverse events known to be associated with increased tacrolimus exposure.

At 24 months in de novo kidney transplant recipients, 98 % of tacrolimus PR and 98 % of tacrolimus IR recipients had at least one adverse event; serious adverse events occurred in 62 and 67 % [26].

In de novo liver transplant recipients, there were no significant differences in adverse events between recipients of tacrolimus PR and those receiving tacrolimus IR [21].

As might be expected, in the noncomparative conversion trial in stable liver transplant patients previously receiving tacrolimus IR, the rates of treatment-related adverse events were higher following the conversion (25 vs. 0 % with tacrolimus PR vs. IR) (comparisons were between 14 days on tacrolimus PR and 7 days on tacrolimus IR, with a 30-day follow-up period); however, most adverse events were of mild to moderate severity, and only one (fatigue) occurred in $\geq$ 10 % of patients in either treatment period (10 vs. 0 %; includes both treatment-related and -unrelated adverse events) [20]. Two patients discontinued treatment as a result of adverse events, and there were no treatment-related serious adverse events. During the 50-week extension period, 20 % of tacrolimus PR recipients experienced at least one treatment-related adverse event, the most common adverse events were fatigue and headache (both 16 %; includes both treatment-related and -unrelated adverse events), one patient had a potentially treatment-related serious adverse event (rejection), and three patients discontinued treatment as a result of adverse events.

A noncomparative, phase IIIb, exploratory trial ($n = 38$) was conducted to investigate the effect of switching kidney transplant recipients receiving tacrolimus IR and experiencing tremor (a common adverse event with tacrolimus treatment) to treatment with tacrolimus PR, hypothesizing that the lower tacrolimus C_{max} may reduce tremor severity [30]. Switching to tacrolimus PR was associated with a significant improvement in tremor [mean absolute change of −5.35 in Fahn–Tolosa–Marin rating scale (FTM) score (primary endpoint; central, blinded reading); $p < 0.0001$] and in postural tremor amplitude in the dominant hand of 36 patients ($p < 0.05$). Moreover, health-related quality of life was improved [79 % of patients reported improvement in Patient Global Impression of Improvement scale score ($p < 0.0005$) and there was a mean absolute change on Quality of Life in Essential Tremor scale (QUEST) score of −7.04 ($p < 0.001$)] after the switch [30]. Change in QUEST score was significantly correlated with change in FTM score ($r = 0.44$; $p = 0.006$) [31].

Data are limited from pregnant organ transplant recipients being treated with tacrolimus [16]. There is currently no evidence of an increased risk of adverse events affecting the course and outcome of pregnancy; however, spontaneous abortion has been reported, and there is a risk for premature delivery (<37 weeks) (most newborns had normal birth weight for their gestational age) and newborn hyperkalaemia (normalized spontaneously).

There is limited experience with tacrolimus overdosage, and no direct experience with tacrolimus PR overdosage [16]. Symptoms of tacrolimus overdosage may include tremor, headache, nausea, vomiting, infection, urticaria, lethargy, and increased blood urea nitrogen, serum creatinine and ALT levels. Tacrolimus is unlikely to be dialyzable. Tacrolimus may cause visual and neurological disturbances; these may be enhanced if alcohol is coadministered [16].

Medication errors (e.g. inadvertent, unintentional or unsupervised substitution of different formulations of tacrolimus) have been reported, and have on occasion led to transplant rejection [16]. Allergic and anaphylactoid reactions, gastrointestinal perforation, cardiac disorders (ventricular hypertrophy or hypertrophy of the septum), and pure red cell aplasia (PRCA) (in patients with risk factors, underlying disease or concomitant medication associated with PRCA) have been observed in tacrolimus recipients [16].

6 Dosage and Administration

In the EU, oral tacrolimus PR (Envarsus®) tablets are approved for the prophylaxis of transplant rejection in adult kidney or liver allograft recipients and the treatment of

allograft rejection that is resistant to other immunosuppressive drugs in adult patients [16].

The recommended starting dosage for tacrolimus PR in de novo kidney or liver transplant recipients is 0.17 or 0.11–0.13 mg/kg, respectively, once daily in the morning, initiated within 24 h of the completion of surgery [16]. Kidney or liver transplant recipients being converted from maintenance treatment with tacrolimus IR or the earlier prolonged-release formulation of tacrolimus (Advagraf®) should be converted using a dose conversion multiplier of 0.7 for the total daily dose, taken once daily in the morning [16].

The dosage may vary, depending on the immunosuppressive regimen chosen [16]. As there is large inter-individual pharmacokinetic variation with tacrolimus [32], the dosage should be based on clinical assessments (rejection and tolerability) and whole-blood tacrolimus concentration monitoring [2, 16]. Clinical trial data suggest that the optimum whole-blood tacrolimus C_{trough} should generally be in the range of 5–20 ng/mL in de novo kidney transplant recipients and 5–15 ng/mL in subsequent maintenance therapy [2, 16]; however, the European consensus conference on optimization of tacrolimus therapy suggested that a lower target C_{trough} may be more appropriate in maintenance therapy (5–10 ng/mL, with concomitant treatment) [33]. The dosage of tacrolimus PR is expected to be reduced in the post-transplant period [16]. Tacrolimus concentrations may be influenced by many factors, such as patient characteristics, concomitant immunosuppressive medication, pharmacogenetics, and certain adverse events [33–35]. For example, Black patients may require a higher dosage to achieve the target C_{trough}; when converting from tacrolimus IR in clinical trials, the dose conversion multiplier in Black patients was 0.85 [16]. Tacrolimus PR is not interchangeable with other tacrolimus formulations on an equal dose-by-dose basis [16].

Increased tacrolimus PR dosages may be necessary in the case of rejection episodes, as may supplemental corticosteroid therapy and short courses of mono- or polyclonal antibodies [16].

Patients with severe hepatic impairment may require dosage reduction, as tacrolimus is largely metabolized in the liver (see Sect. 3) [16]. No dosage adjustments are required for patients with renal impairment; however, as tacrolimus has nephrotoxic potential, careful monitoring of renal function is recommended. Several potential drug interactions have been reported with tacrolimus treatment (see Sect. 3.1); the tacrolimus PR dosage may need to be adjusted when it is coadministered with certain drugs [16]. The combination of ciclosporin and tacrolimus is not recommended [16]. Tacrolimus-based treatment is generally initiated 12–24 h after ciclosporin discontinuation.

Local prescribing information should be consulted for further, detailed information, including therapeutic drug monitoring recommendations, contraindications, precautions, drug interactions, and use in special patient populations.

7 Current Status of Tacrolimus Prolonged Release (Envarsus®) in Kidney and Liver Transplant Recipients

Oral tacrolimus PR (Envarsus®) tablets are indicated for the prophylaxis and treatment (if rejection is resistant to other immunosuppressive drugs) of transplant rejection in adult kidney and liver allograft recipients, in the EU [16].

In phase III clinical trials, tacrolimus PR was noninferior to tacrolimus IR in both de novo and stable, previously treated kidney transplant recipients, and had a similar tolerability profile. Preliminary efficacy data from phase II trials in de novo and stable, previously treated liver transplant recipients imply that tacrolimus PR is effective in these patient groups; however, more data would be of great interest. Pharmacokinetic analyses demonstrated that tacrolimus PR is associated with a higher bioavailability, reduced peak-trough concentration fluctuation ratio, lower mean values for percentage degree of fluctuation and percentage degree of swing, and a longer time to C_{max} than both tacrolimus IR and an earlier prolonged-release formulation of tacrolimus (Advagraf®). Further investigation into potential inter-formulation clinical differences, particularly with regard to pharmacokinetics, efficacy and tolerability, would be of great interest; there are plans to initiate several additional studies comparing tacrolimus PR with existing therapies [36]. More information on treatment adherence would also be of interest. Tacrolimus PR is a promising addition to the treatment options available for kidney and liver transplant recipients.

Data selection sources: Relevant medical literature (including published and unpublished data) on Tacrolimus prolonged release (Envarsus) was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 9 January 2014], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Tacrolimus, extended release, prolonged release, once daily, Envarsus, LCP-Tacro, kidney, renal, transplant*.
Study selection: Studies in patients with kidney transplant rejection who received Tacrolimus prolonged release. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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References

1. Baker R, Jardine A, Andrews P. Renal Association Clinical Practice Guideline on post-operative care of the kidney transplant recipient. Nephron Clin Pract. 2011;118(Suppl 1):c311–47.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9(Suppl. 3):S1–157.
3. Barraclough KA, Isbel NM, Johnson DW, et al. Once- versus twice-daily tacrolimus: are the formulations truly equivalent? Drugs. 2011;71(12):1561–77.
4. Butler JA, Roderick P, Mullee M, et al. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. Transplantation. 2004;77(5):769–76.
5. Weng FL, Israni AK, Joffe MM, et al. Race and electronically measured adherence to immunosuppressive medications after deceased donor renal transplantation. J Am Soc Nephrol. 2005;16(6):1839–48.
6. Kuypers DR, Peeters PC, Sennesael JJ, et al. Improved adherence to tacrolimus once-daily formulation in renal recipients: a randomized controlled trial using electronic monitoring. Transplantation. 2013;95(2):333–40.
7. Hardinger KL, Brennan DC. Novel immunosuppressive agents in kidney transplantation. World J Transplant. 2013;3(4):68–77.
8. Ho ETL, Wong G, Craig JC, et al. Once-daily extended-release versus twice-daily standard-release tacrolimus in kidney transplant recipients: a systematic review. Transplantation. 2013;95(9):1120–8.
9. Gaber AO, Alloway RR, Bodziak K, et al. Conversion from twice-daily tacrolimus capsules to once-daily extended-release tacrolimus (LCPT): a phase 2 trial of stable renal transplant recipients. Transplantation. 2013;96(2):191–7.
10. Budde K, Bunnapradist S, Grinyo JM, et al. Novel once-daily extended-release tacrolimus (LCPT) versus twice-daily tacrolimus in de novo kidney transplants: one-year results of phase III, double-blind, randomized trial. Am J Transplant. 2014;14(12):2796–806.
11. Cross SA, Perry CM. Tacrolimus once-daily formulation: in the prophylaxis of transplant rejection in renal or liver allograft recipients. Drugs. 2007;67(13):1931–43.
12. Scott LJ, McKeage K, Keam SJ, et al. Tacrolimus: a further update of its use in the management of organ transplantation. Drugs. 2003;63(12):1247–97.
13. Plosker GL, Foster RH. Tacrolimus: a further update of its pharmacology and therapeutic use in the management of organ transplantation. Drugs. 2000;59(2):323–89.
14. Spencer CM, Goa KL, Gillis JC. Tacrolimus. An update of its pharmacology and clinical efficacy in the management of organ transplantation. Drugs. 1997;54(6):925–75.
15. Peters DH, Fitton A, Plosker GL, et al. Tacrolimus. A review of its pharmacology, and therapeutic potential in hepatic and renal transplantation. Drugs. 1993;46(4):746–94.
16. European Medicines Agency. Envarsus® (tacrolimus extended-release tablets): EU summary of product characteristics. 2014. http://www.ema.europa.eu/. Accessed 17 Sept 2014.
17. European Medicines Agency. Envarsus® (tacrolimus extended-release tablets): CHMP assessment report. 2014. http://www.ema.europa.eu/. Accessed 19 Dec 2014.
18. Nigro V, Glicklich A, Weinberg J. Improved bioavailability of MELTDOSE once-daily formulation of tacrolimus (LCP-Tacro) with controlled agglomeration allows for consistent absorption over 24 hrs: a scintigraphic and pharmacokinetic evaluation [abstract no. B1034]. In: American Transplant Congress; 2013.
19. Nigro V, Glicklich A, Weinberg J. Flexible dosing of once-daily LCP-Tacro tablets: morning vs. evening randomized crossover chronopharmacokinetic study [abstract plus poster]. In: European Society for Organ Transplantation/American Society of Transplantation 2012 joint meeting; 2012.
20. Alloway RR, Eckhoff DE, Washburn KW, et al. Conversion from twice daily tacrolimus capsules to once daily extended-release tacrolimus (LCP-Tacro): phase 2 trial of stable liver transplant recipients. Liver Transpl. 2014;20(5):564–75.
21. Feng S, Chapman WC, DuBay D. A phase 2 randomized study of the pharmacokinetics, safety and efficacy of LCP-Tacro™ tablets once-a-day vs. Prograf® capsules twice-a-day in de novo liver transplants [abstract no. 709]. Am J Transplant. 2012;12(Suppl. s3):239.
22. Alloway R, Mulgaonkar S, Ueda K, et al. A phase 2 randomized study of the pharmacokinetics, safety and efficacy of LCP-Tacro tablets once-a-day vs Prograf capsules twice-a-day in de novo kidney transplants [abstract no. 1106]. Am J Transplant. 2011;11(Suppl. 2):355.
23. Nigro V, Glicklich A, Weinberg J. Improved bioavailability and pharmacokinetics of tacrolimus with novel once-daily Lcp-Tacro™ meltdose formulation versus once-daily Advagraf® capsules [abstract plus poster]. In: European Society for Organ Transplantation/American Society of Transplantation 2012 joint meeting; 2012.
24. Bunnapradist S, Ciechanowski K, West-Thielke P, et al. Conversion from twice-daily tacrolimus to once-daily extended release tacrolimus (LCPT): the phase III randomized MELT trial. Am J Transplant. 2013;13(3):760–9.
25. Mulgaonkar S. LCP-Tacro demonstrated significantly fewer dose adjustments: results of a phase 2 randomized study of LCP-Tacro (MeltDose once-daily prolonged release tacrolimus tablets) vs. Prograf® capsules twice-a-day in de novo kidney transplant patients [abstract no. PP IS-C22]. In: European Society for Organ Transplantation + American Society of Transplantation meeting; 2014.
26. Rostaing L, Ciechanowski K, Bunnapradist S, et al. Two-year results of Envarsus (once-daily MeltDose tacrolimus tablets) vs Prograf (twice-daily tacrolimus capsules): a phase 3, double-blind, double-dummy, multi-center, prospective, randomized study. [abstract no. A2978 plus poster]. Am J Transplant. 2014;14(Suppl. 3):661–2.
27. Bunnapradist S, Alloway R, West-Thielke P, et al. Lower treatment failures in Blacks and older de novo and stable kidney transplant recipients treated with Envarsus once-daily MeltDose tablets vs. twice-daily Prograf capsules: a pooled subgroup analysis of two phase 3 trials [abstract no. A211 plus poster]. Am J Transplant. 2014;14(Supp(3)):459–60.
28. Budde K, Silva H, Steinberg S, et al. Higher initial exposure of Envarsus immediately post transplantation is not associated with increased risk of delayed graft function in kidney transplant patients treated with novel once-daily MeltDose tacrolimus (Envarsus) vs. twice-daily tacrolimus (Prograf): results from a phase 3, double-blind, double-dummy, multi-center, randomized trial [abstract no. A212]. Am J Transplant. 2014;14(Suppl. 3):460.
29. Silva TH Jr, Bunnapradist S, Steinberg S. Higher starting dose and rapid attainment of tacrolimus blood levels with Envarsus vs. Prograf is not associated with increased toxicity: exploratory analysis of a phase 3, double-blind, double-dummy, multi-center, randomized, prospective study of Envarsus (once-daily MeltDose tacrolimus tablets) vs. Prograf (twice-daily tacrolimus capsules). [abstract no. A207]. Am J Transplant. 2014;14(Suppl. 3):458.

30. Morgan J, Langone A, Nigro V, et al. Tacrolimus-induced tremor: switching from immediate-release (IR-TAC) to LCP-Tacro extended-release tacrolimus (LCPT) reduces tremor and improves quality of life [abstract no. P4.072]. Neurology. 2014;82(10 Suppl. 1).
31. Gedaly R, Steinberg SM, Langone A, et al. LCP-Tacro-associated improvement in tacrolimus-induced tremors is also associated with improvement in quality of life: results of a switching study of kidney transplant patients with tremor (Strato) [abstract no. P508]. In: 16th Congress of the European Society for Organ Transplantation; 2013.
32. van Rossum HH, de Fijter JW, van Pelt J. Pharmacodynamic monitoring of calcineurin inhibition therapy: principles, performance, and perspectives. Ther Drug Monit. 2010;32(1):3–10.
33. Wallemacq P, Armstrong VW, Brunet M, et al. Opportunities to optimize tacrolimus therapy in solid organ transplantation: report of the European consensus conference. Ther Drug Monit. 2009;31(2):139–52.
34. de Jonge H, Naesens M, Kuypers DR. New insights into the pharmacokinetics and pharmacodynamics of the calcineurin inhibitors and mycophenolic acid: possible consequences for therapeutic drug monitoring in solid organ transplantation. Ther Drug Monit. 2009;31(4):416–35.
35. Provenzani A, Santeusanio A, Mathis E, et al. Pharmacogenetic considerations for optimizing tacrolimus dosing in liver and kidney transplant patients. World J Gastroenterol. 2013;19(48):9156–73.
36. Veloxis Pharmaceuticals. Envarsus® development strategy and status. 2014. http://www.veloxis.com/devStrategy.cfm. Accessed 13 Oct 2014.