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Tacrolimus Once-Daily Formulation

In the Prophylaxis of Transplant Rejection in Renal or Liver Allograft Recipients

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Contents

Abstract

▲ Tacrolimus once-daily (OD) is a new oral formulation of the well established immunosuppressant tacrolimus.

▲ Tacrolimus OD provided equivalent steady-state systemic tacrolimus exposure to that achieved with standard oral tacrolimus twice daily in stable renal and liver transplant recipients. The two formulations also provided broadly similar steady-state systemic exposure in *de novo* renal and liver transplant recipients.

▲ In a large, randomised, nonblind, multicentre, three-armed, noninferiority trial in *de novo* renal transplant recipients, the efficacy failure rates (primary endpoint) [any patient who died, experienced graft failure, had a biopsy-confirmed acute rejection or was lost to follow-up] of tacrolimus OD (14.0%) and standard tacrolimus (15.1%) were noninferior to that of ciclosporin (cyclosporine) microemulsion (17.0%) at 1 year, when each was given in conjunction with corticosteroids, mycophenolate mofetil and basiliximab induction.

▲ Data from a pharmacokinetic study suggests that tacrolimus OD has similar efficacy to standard tacrolimus in *de novo* liver transplant recipients over 6 weeks of treatment.

▲ In noncomparative 2-year trials, tacrolimus OD was effective in stable renal and liver transplant recipients converted to tacrolimus OD from standard tacrolimus.

▲ The overall tolerability profile of tacrolimus OD appears to be similar to that of standard tacrolimus in *de novo* and stable renal and liver transplant patients.

Features and properties of tacrolimus once-daily (OD) formulation (Advagraf®)	
Indication	
Prophylaxis of allograft rejection in adult renal and liver transplant recipients	
Mechanism of action	
Inhibition of T-cell activation	
Dosage and administration	
Initial dosage in *de novo* transplant recipients	
De novo renal transplant patients	0.20–0.30 mg/kg/day
De novo liver transplant patients	0.10–0.20 mg/kg/day
Patients maintained on twice-daily standard tacrolimus can be converted to tacrolimus OD at the same total daily dose	
Route of administration	Oral
Frequency of administration	OD in the morning
Pharmacokinetic profile in adults (mean log transformed steady-state values converted to original scale)	
Maximum whole-blood concentration	
Stable renal transplant patients (median dosage 6.0 mg/day)	13.5 ng/mL
Trough whole-blood concentration	
Stable renal transplant patients (median dosage 6.0 mg/day)	5.7 ng/mL
Stable liver transplant patients (median dosage 4.0 mg/day)	5.4 ng/mL
Area under the whole-blood concentration-time curve from time 0 to 24h	
Stable renal transplant patients (median dosage 6.0 mg/day)	192.3 ng • h/mL
Stable liver transplant patients (median dosage 4.0 mg/day)	176.6 ng • h/mL
Terminal elimination half-life (healthy volunteers receiving 4 mg/day)	37.8h
Treatment-emergent adverse events	
Most frequent (>5%), occurring significantly more frequently in *de novo* renal transplant patients treated with tacrolimus OD than in recipients of ciclosporin microemulsion	Diarrhoea, tremor, diabetes mellitus, orthostatic hypotension, sinusitis, gastroenteritis, alopecia

Tacrolimus is a well established calcineurin inhibitor used for long-term prevention of allograft rejection in solid organ and bone marrow transplantation.[1] In solid organ transplantation, lifelong immunosuppression is required to maintain graft function;[1] however, noncompliance has been reported in 1.4–66.7% of adult renal transplant patients.[2] A meta-analysis found nonadherent renal transplant patients had a 7-fold increase in the odds of graft failure.[2] Once-daily dosing of immunosuppressants was associated with increased adherence over twice-daily dosing in renal transplant patients.[3]

Tacrolimus once-daily (OD) formulation (extended release tacrolimus, modified release tacrolimus, MR4) [Advagraf® [1] prolonged-release hard capsules[4]] offers the benefit of once-daily administration over other formulations of calcineurin inhibitors, such as standard tacrolimus[5,6] or ciclosporin (cyclosporine) microemulsion[7] (hereafter referred to as ciclosporin) formulations, which require twice-daily administration. This profile provides a brief overview of the pharmacodynamics of tacrolimus and focuses on the pharmacokinetics and clinical profile of tacrolimus OD in the prophylaxis of allograft rejection in renal and liver transplant patients.

1. Pharmacodynamic Profile

The pharmacodynamic profile of tacrolimus is well established and has been reviewed elsewhere.[1,8] Therefore, this section provides a brief overview.

- Tacrolimus, a macrolide immunosuppressant, inhibits cellular immune responses and humoral immune responses to a lesser extent.[1] Cell-mediated immune responses, such as allograft rejection, delayed type hypersensitivity, collagen-induced arthritis, experimental allergic encephalomyelitis and graft-versus-host-disease were suppressed by tacrolimus in animals.[6]
- The key mechanism of tacrolimus in preventing the immune response involved in allograft rejection appears to be inhibition of T-cell activation.[1,6] Tacrolimus forms a complex with the immunophilin FK506 binding protein 12, which blocks the phosphatase activity of calcineurin.[1] This prevents assorted nuclear factors (such as nuclear factor of activated T cells) from being translocated to the nucleus so that transcription of early T-cell activation genes is suppressed and production of cytokines, including interleukin-2 (IL-2), is blocked.[8]
- IL-2 mediates the proliferation of helper T cells,[1] which play a pivotal role in allograft rejection[1] through interaction with the effector cells of rejection.[9] In particular, the formation of cytotoxic T cells, mainly responsible for allograft rejection, is inhibited by tacrolimus.[4]
- Important cytokines for the cell-mediated response, which are produced by T helper-1 cells, are preferentially suppressed by tacrolimus over cytokines involved in the stimulation of B cells and production of antibodies, which are produced by T helper-2 cells.[8] Tacrolimus inhibits T cell-dependent B-cell activation and proliferation and calcium-dependent B-cell activation.[8]
- Tacrolimus inhibits several immune responses with 10–100-fold the potency of ciclosporin, which forms a complex with a different binding protein, cyclophilin A.[1] Effects on T-cell receptor expression,[10] T helper-2 cell cytokine expression and some features of humoral immunity appear to differ between ciclosporin and tacrolimus.[8] Interstitial infiltration by T lymphocytes and monocytes/macrophages was significantly lower in renal allograft protocol biopsies obtained from patients treated with tacrolimus than in those obtained from patients treated with ciclosporin.[11]
- As with ciclosporin, tacrolimus can cause nephrotoxicity.[1] Possible mechanisms of tacrolimus-induced nephrotoxicity include cyclic adenosine monophosphate-dependent signalling modulation, nuclear factor-κB activation, increased endothelin levels and/or thromboxane A_2 or increased expression of genes associated with fibrosis, such as transforming growth factor-β, collagen and proteolytic matrix metalloproteinases.[1]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

• Other pharmacodynamic properties of tacrolimus include diabetogenic (e.g. insulin sensitivity and β-cell secretory reserve were significantly decreased and the β-cell/α-cell axis was impaired in liver transplant patients receiving tacrolimus[12]), cardiovascular (e.g. appears to be less lipogenic than ciclosporin in transplant patients) and neurological effects (e.g. increases apoptosis in brain capillary epithelial cells).[1] These may contribute to adverse reactions and potential benefits of tacrolimus as well as pharmacodynamic interactions.

• In *de novo* renal transplant patients treated with tacrolimus OD, standard tacrolimus or ciclosporin, each in combination with mycophenolate mofetil, corticosteroids and basiliximab induction (see section 3), mean total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) in evaluable patients after 1 year of treatment were significantly lower in both the tacrolimus OD and standard tacrolimus groups than in the ciclosporin group.[13]

• Mean TC levels at baseline were 143.4, 143.4 and 143.7 mg/dL (3.71, 3.71 and 3.72 mmol/L), while values after 1 year of treatment were 188.7, 182.2 and 202.3 mg/dL (4.88, 4.71 and 5.23 mmol/L) [both $p \leq 0.02$ vs ciclosporin] for the tacrolimus OD, standard tacrolimus and ciclosporin groups, respectively.[13] After 2 years of treatment (preliminary data available as an abstract),[14] corresponding values were 182.2, 177.2 and 186.9 mg/dL (4.71, 4.58 and 4.83 mmol/L) [statistical analyses not reported].

• At baseline, mean LDL-C levels for the tacrolimus OD, standard tacrolimus and ciclosporin groups were 80.1, 79.9 and 80.6 mg/dL (2.07, 2.07 and 2.08 mmol/L), respectively.[13] Corresponding values after 1 year of treatment were 102.4, 97.1 and 113.4 mg/dL (2.65, 2.51 and 2.93 mmol/L) [both $p \leq 0.020$ vs ciclosporin].[13] After 2 years of treatment, corresponding values were 95.8, 102.7 and 100.7 mg/dL (2.48, 2.66 and 2.60 mmol/L) [statistical analyses not reported].[14]

• There were no significant between-group differences in high-density lipoprotein-cholesterol (HDL-C) or triglyceride levels.[13] Mean HDL-C levels at baseline were 42.3, 44.4 and 42.5 mg/dL (1.09, 1.15 and 1.10 mmol/L), while values at 1 year were 51.5, 52.2 and 51.9 mg/dL (1.33, 1.35 and 1.34 mmol/L) in the tacrolimus OD, standard tacrolimus and ciclosporin groups, respectively.[13] Mean triglyceride levels at baseline were 111.4, 99.2 and 96.6 mg/dL (1.26, 1.12 and 1.09 mmol/L) and were 183.9, 176.8 and 195.7 mg/dL (2.08, 2.00 and 2.21 mmol/L), respectively, after 1 year of treatment.[13]

• In patients with TC levels <300 mg/dL (<7.76 mmol/L) at baseline, after 1 year of treatment, the incidence of TC ≥300 mg/dL was significantly lower in the tacrolimus OD group and the standard tacrolimus group than in the ciclosporin group (4.8% and 3.4% vs 10.8%; $p = 0.011$ for both comparisons).[13]

• During the first year of the study, lipid-lowering medication was received by 50.9%, 44.8% and 60.8% of tacrolimus OD, standard tacrolimus and ciclosporin recipients, respectively.[13] After 2 years of treatment, the proportion of patients receiving lipid-lowering medication was significantly lower ($p \leq 0.036$) in the tacrolimus OD and standard tacrolimus groups than in the ciclosporin group (48.4% and 49.0% vs 62.1%).[14]

• Some glucose metabolism disorder parameters, not considered adverse events by the study's investigators, in patients with no history of diabetes mellitus at baseline were affected to a greater extent in patients receiving tacrolimus than in those receiving ciclosporin.[13] During the first year of treatment, the incidence of a single fasting plasma glucose ≥126 mg/dL (≥6.99 mmol/L) was not significantly different in the tacrolimus OD group from that in the ciclosporin group (56.4% vs 52.6%); however, the incidence was significantly higher in the standard tacrolimus group (64.0%) than in the ciclosporin group ($p \leq 0.05$).[13]

• New onset insulin use for ≥30 days, during the first year of treatment, was not significantly different for either the tacrolimus OD group or the standard tacrolimus group compared with the ciclosporin group (5.5% and 6.0% vs 2.6%). However, new use of oral antihyperglycaemics, during the first year of treatment, was significantly higher ($p \leq 0.05$) in the tacrolimus OD group and the

standard tacrolimus group than in the ciclosporin group (14.1% and 10.0% vs 3.3%).[13] Between years 1 and 2, there were no new cases of insulin-dependent diabetes (no other glucose metabolism disorders were reported).[14]

- It should be noted that in the aforementioned trial, patients also received corticosteroids,[13] which are associated with increases in LDL-C and HDL-C, are positively correlated with serum triglycerides, disturb glucose tolerance and play a significant role in the development of post-transplant diabetes.[15]
- Pharmacodynamic interactions, manifest as increased nephrotoxic or neurotoxic effects, may occur between tacrolimus and coadministered drugs known to have such effects, such as aciclovir, aminoglycosides, cotrimoxazole, ganciclovir, gyrase inhibitors, NSAIDs and vancomycin.[4] Tacrolimus may be associated with hyperkalaemia; therefore high potassium intake or potassium-sparing diuretics should be avoided. In addition, during treatment with tacrolimus, vaccinations may be less effective and the use of live attenuated vaccines should be avoided.[4]

2. Pharmacokinetic Profile

The pharmacokinetics of tacrolimus OD in adult renal[16,17] and liver[18,19] transplant recipients and paediatric liver transplant recipients[20] are reviewed in this section, supplemented with data from healthy volunteers.[21] For completeness, information on the pharmacokinetics of standard tacrolimus is included where there are no available data specific to tacrolimus OD.

Adult data have been obtained from patients with stable renal (evaluable n = 66)[17] or liver transplants (evaluable n = 62)[19] in nonblind, multicentre studies with a single-sequence crossover design and *de novo* renal (n = 66)[16] or liver (n = 77)[18] transplant recipients in randomised, nonblind, multicentre studies (available as abstracts). Supplementary data were obtained from the European Medicines Agency (EMEA) scientific discussion, which also includes limited data on two further studies in stable renal transplant patients (evaluable n = 35 and 60),[21] and the manufacturer's prescribing information.[4] Paediatric data have been obtained from stable liver transplant recipients in a nonblind, multicentre study (n = 18).[20] Where available, study design details are discussed in section 3. Reported parameters were determined from whole-blood tacrolimus concentrations (R Alloway, personal communication).[16-20,22] The equivalence of pharmacokinetic parameters was established based on the 90% confidence interval for the ratio of the natural logarithm-transformed parameters of tacrolimus OD being within 80% and 125% of standard tacrolimus.[17,19-21] Parameters reported from the fully published studies were calculated by transforming natural log means back to the original (linear) scale, where clearly stated.[17,19,20]

- When stable renal and liver transplant recipients were converted from standard tacrolimus to the same total daily dose of tacrolimus OD, ≈70%[17] or 80%[19] of patients did not require subsequent dose adjustments. Dose adjustments were required for dosing errors, management of adverse events, maintenance of trough concentrations (C_{min}) or at the physician's discretion.[17,19]
- In the prescribing information, the values for the area under the concentration-time curve from time 0 to 24 hours (AUC_{24}) were reported to be ≈10% lower in stable patients following conversion to tacrolimus OD; therefore, C_{min} monitoring and dose adjustments are recommended to ensure similar systemic exposure is maintained.[4]
- In stable renal transplant patients, equivalence before and after conversion from standard tacrolimus to tacrolimus OD was demonstrated for tacrolimus AUC_{24} and C_{min} values in three studies[17,21] as well as maximum concentration (C_{max}) values in one of these studies.[17] In one study, patients were converted from a median total dosage of standard tacrolimus 5.0 mg/day to tacrolimus OD 5.0 mg/day, which was increased to 6.0 mg/day at steady state; at steady state, the mean AUC_{24} was 202.5 versus 192.3 ng • h/mL, the mean C_{min} was 6.6 versus 5.7 ng/mL and the mean C_{max} was 15.3 versus 13.5 ng/mL.[17] In the EMEA scientific discussion, no mean data are provided for the two other

studies but 90% confidence interval values indicate equivalence for AUC_{24} and C_{min}.[21]

- In stable liver transplant patients at steady state, tacrolimus AUC_{24}, but not C_{min},[21] values were equivalent before versus after conversion from a median dosage of standard tacrolimus of 4.0 mg/day to tacrolimus OD 4.0 mg/day;[19] mean AUC_{24} values were 199.0 versus 176.6 ng • h/mL,[22] mean C_{min} values were 6.5 versus 5.4 ng/mL.[19]

- The mean AUC_{24} after the first day of treatment, at a total daily dose of tacrolimus 0.20 mg/kg, was 260 ng • h/mL in *de novo* renal transplant recipients who received tacrolimus OD and 320 ng • h/mL in those who received two divided doses of standard tacrolimus.[16] Dose-normalised geometric mean AUC_{24} ratios for tacrolimus OD to standard tacrolimus were 0.66 at day 1, but steady state ratios were 0.98 and 0.82 at day 14 and day 42.[21]

- After the first day of treatment with tacrolimus 0.10–0.15 mg/kg/day, *de novo* liver transplant recipients who received tacrolimus OD had a mean AUC_{24} of 150 ng • h/mL and those who received two divided doses of standard tacrolimus had a mean AUC_{24} of 260 ng • h/mL.[18] Dose-normalised geometric AUC_{24} ratios for tacrolimus OD to standard tacrolimus were 0.48, 0.88 and 0.91 after 1, 14 and 42 days, respectively.[21] See the Therapeutic Drug Monitoring section for further details.

- In healthy volunteers, tacrolimus OD demonstrated dose-linearity in the dose range of 1.5–10mg.[21] At steady state, in healthy volunteers administered tacrolimus OD 4 mg/day, the median time to C_{max} (t_{max}) was 2 hours.[21]

- AUC values for tacrolimus OD show less intraindividual variability than those for standard tacrolimus. In stable liver transplant recipients, intraindividual variability for dose-corrected tacrolimus exposure was significantly lower with tacrolimus OD than with standard tacrolimus (ratio = 0.594; p = 0.044).[19]

- The presence of food reduces the rate and extent of absorption of tacrolimus.[1] In healthy volunteers, administration of tacrolimus OD following a high fat meal, compared with the fasted state, reduced mean AUC_{24} and C_{max} by ≈25% and increased t_{max} from 2 to 3.5 hours.[21]

- Tacrolimus displays time-dependent changes in its pharmacokinetic profile.[23,24] Diurnal variations in tacrolimus pharmacokinetics have also been observed.[23-25] In a single-dose study in healthy volunteers, administration of tacrolimus OD in the evening, compared with in the morning, reduced the AUC from time 0 to infinity by 35%.[21]

- The bioavailability of tacrolimus is decreased in a greater proportion of Asian, African American and Hispanic patients than Caucasian patients;[1] in order to achieve the same concentrations African American patients require higher milligram per kilogram dosages of standard tacrolimus than Caucasians.[23]

- Tacrolimus OD appeared to provide equivalent tacrolimus exposure to standard tacrolimus regardless of gender or diabetes status in stable liver transplant recipients[19] and regardless of gender, race or diabetes status in stable renal transplant recipients.[17]

- Tacrolimus is strongly bound to erythrocytes[4] and the distribution between plasma and blood varies widely,[1] although blood concentrations are significantly higher than plasma concentrations.[23] Protein binding in plasma, mostly to α_1-acid glycoprotein and albumin, is high (up to 99%).[1]

- Tacrolimus is widely distributed with a volume of distribution of 1.41 L/kg and 0.85 L/kg in renal and liver transplant recipients receiving intravenous tacrolimus.[1] Human data demonstrate that tacrolimus crosses the placenta and is distributed into breast milk.[4]

- Tacrolimus is predominantly metabolised in the liver and to a lesser extent in the intestinal mucosa by cytochrome P450 (CYP) 3A4.[1] In the intestinal mucosa, metabolism by P-glycoprotein is also involved.[1] Metabolism is extensive with <0.5% of the unchanged parent drug being excreted in faeces or urine.[23] The main metabolite, 13-*O*-demethyltacrolimus, has ≈10% of the immunosuppressive activity of tacrolimus.[23]

- Elimination of tacrolimus metabolites is predominantly via the biliary route (>95%)[23] with

excretion in faeces.[1] Urinary excretion accounts for a small proportion of tacrolimus elimination.[23]

- Clearance of tacrolimus is low. In adult kidney and liver transplant recipients, tacrolimus clearance was 6.7 L/h and 4.1 L/h.[4]
- In healthy volunteers, the mean terminal elimination half-life at steady state after 10 days' administration of tacrolimus OD 4 mg/day was 37.8 hours.[21]
- Genetic differences in CYP3A expression appear to play a role in the interindividual variability of tacrolimus pharmacokinetics.[23,26-28] Inconsistent findings on the role of genetic differences in P-glycoprotein expression have been reported.[23,26-28] However, interindividual variability was lower in *de novo* renal and liver transplant recipients receiving tacrolimus OD than in those receiving standard tacrolimus.[16,18]
- A number of pharmacokinetic interactions of potential clinical significance between tacrolimus and other drugs have been reported.[1,4] Tacrolimus blood concentrations may be increased by CYP3A4 inhibitors and other drugs, and may be decreased by CYP3A4 and P-glycoprotein inducers and other drugs.[1,4] Tacrolimus may be displaced from its binding proteins when other drugs that are highly protein bound are coadministered.[21]
- In stable paediatric liver transplant recipients,[20] tacrolimus OD was equivalent to standard tacrolimus based on AUC_{24} and C_{min}. Tacrolimus exposure was equivalent in subgroup analyses for black, white and female recipients but not for male recipients, although this may be reflective of the small sample size and interindividual variability. In addition, there was good correlation between AUC_{24} and C_{min} for both tacrolimus OD and standard tacrolimus ($r = 0.90$ and 0.94).[20]
- In paediatric patients prior to conversion, after a mean total daily dose of standard tacrolimus 0.184 mg/kg, least-squares mean steady-state values were 179.58 ng • h/mL for AUC_{24} and 5.35 ng/mL for C_{min}.[20] Postconversion, after a mean tacrolimus OD dosage of 0.182 mg/kg/day, corresponding least-squares mean steady-state values were 181.22 ng • h/mL and 4.91 ng/mL.[20]

Therapeutic Drug Monitoring

- Tacrolimus has a narrow therapeutic window and shows high inter- and intraindividual variability in its pharmacokinetic profile[1] with drug doses correlating poorly with blood and plasma concentrations.[23] Therefore, therapeutic drug monitoring (TDM) is required for treatment optimisation.[1]
- It is recommended that whole-blood C_{min} values of tacrolimus are monitored;[1,4-6] however, while high C_{min} values have been correlated with toxicity, there have been conflicting reports regarding low tacrolimus C_{min} values being related to rejection.[23]
- Current therapeutic practices for monitoring tacrolimus concentrations have been suggested to be effective for monitoring tacrolimus OD.[17,19] In *de novo* and stable renal and liver transplant recipients, there was good correlation between AUC and C_{min} at steady state in patients receiving tacrolimus OD ($r = 0.86–0.92$) or standard tacrolimus ($r = 0.80–0.94$).[16-19] In both *de novo* studies, the slope of the line of best fit was similar for both standard tacrolimus and tacrolimus OD, indicating that the same target C_{min} range can be set for both formulations for TDM[21] (see section 5).
- Tacrolimus whole-blood C_{min} values should be monitored frequently in the first 2 weeks post-transplant, prior to conversion to tacrolimus OD and within 2 weeks of conversion, periodically during maintenance treatment, during episodes of diarrhoea, and following dose adjustment, changes in immunosuppressive regimen, or coadministration of substances that may alter tacrolimus whole-blood concentrations.[4] Adjustments in dose may take several days to reach steady state because tacrolimus has a low level of clearance.[4]

3. Therapeutic Efficacy

The efficacy of tacrolimus OD has been assessed in adult *de novo* renal[13,16] or liver[18] transplant recipients, stable renal[29] or liver[30] transplant recipients and paediatric stable liver transplant recipients.[20]

Experience with tacrolimus OD in nonCaucasian patients is limited,[4] where reported, Caucasians

represented 79%[29] or 93%[30] of adult patients and 61.1% of paediatric patients.[20]

Standard tacrolimus has been extensively evaluated in renal and liver transplant patients and has well established efficacy.[1]

Adult *De Novo* Renal Transplant Patients

The efficacy of tacrolimus OD and standard tacrolimus has been compared with that of ciclosporin in *de novo* renal transplant recipients in a randomised, nonblind, multicentre, three-armed, noninferiority phase III trial.[13] One year results are fully published[13] and preliminary results after 2 years of treatment are available as an abstract.[14]

The trial included 638 patients aged 17–77 years receiving a primary or re-transplanted (3.3–4.2%), deceased donor (47.6–51.9%) or non-human leukocyte antigen (HLA)-identical living renal transplant. Most patients had ≥3 HLA mismatches (74.5–81.1%) and were aged <65 years (88.8–90.6%). Exclusion criteria included previously receiving or receiving an organ transplant other than a kidney, receiving a kidney from a non-heart beating, ABO blood group incompatible or ≥60-year-old donor, or a cold ischaemia time of ≥36 hours.[13]

Patients initially received tacrolimus OD 0.15–0.20 mg/kg/day (in the morning) [n = 214], standard tacrolimus 0.075–0.10 mg/kg twice daily (n = 212) or ciclosporin 4–5 mg/kg twice daily (n = 212). Dose adjustment was permitted. Target tacrolimus or ciclosporin whole-blood concentrations were 7–16 ng/mL or 125–400 ng/mL for the first 90 days after transplant, and 5–15 ng/mL or 100–300 ng/mL thereafter. Patients also received corticosteroids, mycophenolate mofetil and basiliximab induction therapy. Crossover was permitted if adverse events or severe refractory rejection led to discontinuation of randomised drug; however, crossover into the tacrolimus OD group was not permitted.[13]

The population for all analyses was a modified intention-to-treat population of all randomised patients who received at least one dose of study drug. A prespecified margin of 10% was used for assessments of noninferiority. All comparisons were against ciclosporin; tacrolimus OD and standard tacrolimus were not directly compared. For patient and graft survival, patients were censored at the time of last follow-up.[13]

The primary endpoint was efficacy failure rate at 1 year, defined as any patient who died, experienced graft failure (return to dialysis for >30 days or re-transplant), had a biopsy-confirmed acute rejection (BCAR) [Banff grade ≥1] or was lost to follow-up (if the patient did not have ≥335 days of follow-up information).[13]

Limited efficacy data for tacrolimus OD compared with standard tacrolimus are also available from a randomised, nonblind, multicentre, pharmacokinetic study in *de novo* renal transplant recipients (see section 2), available as an abstract,[16] with data supplemented from the EMEA scientific discussion.[21]

Patients aged 18–65 years receiving a kidney from a cadaveric or living (not HLA identical) donor were eligible for inclusion; those with high immunological risk (panel reactive antibody grade >50%), significant liver disease or who had received or were about to receive an organ transplant other than a kidney were excluded.[16] In combination with corticosteroids and mycophenolate mofetil,[16,21] patients received tacrolimus OD (n = 60) or standard tacrolimus twice daily (n = 59),[21] at an initial dosage of 0.20 mg/kg/day with target whole-blood C_{min} values of 10–20 ng/mL on days 1 to 14, and 5–15 ng/mL on day 15 to week 6.[16]

- Tacrolimus OD was noninferior to ciclosporin in the three-armed noninferiority trial (figure 1).[13] Efficacy failure rates at 1 year were noninferior to rates in the ciclosporin group (17.0%) for both the tacrolimus OD group (14.0%) and the standard tacrolimus group (15.1%). The differences in efficacy failure rates relative to the ciclosporin group were −3.0% (95.2% CI −9.9, 4.0) for the tacrolimus OD group and −1.9% (95.2% CI −8.9, 5.2) for the standard tacrolimus group.[13]
- For patient and graft survival at 1 year, tacrolimus OD and standard tacrolimus were at least as effective as ciclosporin (figure 1).[13] Differences

in the Kaplan-Meier estimates for 1 year patient survival relative to the ciclosporin group were 1.0% (95% CI −1.6, 3.6) for the tacrolimus OD group and −1.9% (95% CI −5.3, 1.5) for the standard tacrolimus group. Corresponding differences in the Kaplan-Meier estimates for 1 year graft survival relative to the ciclosporin group were 1.0% (95% CI −2.7, 4.6) and −2.9% (95% CI −7.3, 1.6).[13]

- For the incidence of BCAR at 6 and 12 months, tacrolimus OD was not significantly different to ciclosporin, while compared with ciclosporin recipients, a significantly smaller percentage of patients receiving standard tacrolimus experienced BCAR at these timepoints (figure 1).[13]
- Two-year patient survival rates were 97.6%, 93.6% and 96.6% for the tacrolimus OD, standard tacrolimus and ciclosporin groups, respectively (statistical analyses not reported).[14] Corresponding rates for 2-year graft survival were 93.7%, 89.9% and 92.7% (statistical analyses not reported). The between-group difference in the incidence of BCAR at 2 years was not significant. The rates of BCAR at 2 years were 12.9%, 11.1% and 16.6% in the tacrolimus OD, standard tacrolimus and ciclosporin groups, respectively.[14]
- In the pharmacokinetic trial,[16] after 6 weeks of treatment the incidence of BCAR was 13.3% (8 of 60 patients) in patients receiving tacrolimus OD and 15.3% (9 of 59 patients) in patients receiving standard tacrolimus.[21] One patient in the tacrolimus OD group and two patients in the standard tacrolimus group experienced graft loss. Kaplan-Meier estimates for graft survival at 6 weeks were 98.3% for tacrolimus OD recipients and 93.1% for standard tacrolimus recipients.[21]

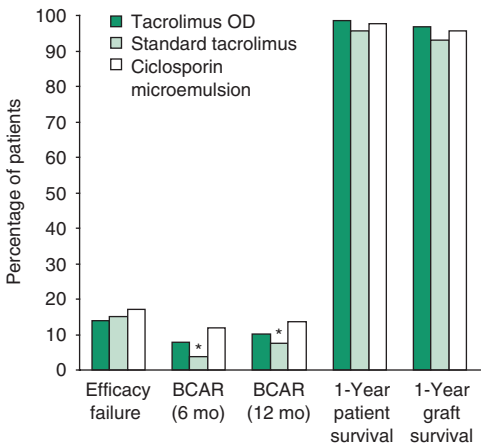

Fig. 1. Efficacy of tacrolimus once-daily (OD) formulation and twice-daily standard tacrolimus compared with twice-daily ciclosporin microemulsion in *de novo* renal transplant recipients also receiving mycophenolate mofetil, corticosteroids and basiliximab induction. Percentage of patients experiencing efficacy failure at 1 year (primary endpoint) or biopsy-confirmed acute rejection (BCAR) [Banff grade ≥1] at 6 months or 1 year and Kaplan Meier estimates for patient and graft survival at 1 year in a large (n = 638) randomised, nonblind, multicentre, phase III trial.[13] Efficacy failure was defined as any patient who died, experienced graft failure (return to dialysis for >30 days or re-transplant), had a BCAR (Banff grade ≥1) or was lost to follow-up (if the patient did not have ≥335 days of follow-up information).[13] * $p \leq 0.04$ vs ciclosporin microemulsion.

Adult Stable Renal Transplant Patients

The efficacy of tacrolimus OD in stable renal transplant patients was assessed in a 2-year noncomparative study,[29] following conversion from standard tacrolimus in a pharmacokinetic study (see section 2).[17]

Patients were converted from twice-daily standard tacrolimus to tacrolimus OD at the same total daily dose.[17] Patients were eligible for inclusion into the initial pharmacokinetic study if they were aged 18–65 years, >6 months post-renal transplant, taking stable doses of tacrolimus twice daily for ≥2 weeks prior to study enrolment and had stable renal function. Exclusion criteria were the receiving of drugs known to interfere with tacrolimus metabolism, rejection within 90 days or requiring antibody therapy for rejection within 6 months prior to the study. Maintenance tacrolimus C_{min} values were 5–15 ng/mL. The mean patient age was 46.9 years.[17]

- After a treatment period of 2 years, 59 of the 67 patients (88%) who received at least one dose of tacrolimus OD remained in the study and were available for follow up.[29] The mean dosage of tacrolimus OD in 58 patients was 6.0 mg/day. Patient survival was 100% (67 of 67 patients), graft survival was 98.5% with 1 of 67 patients experiencing graft loss due to human polyomavirus, and the incidence of BCAR was 6.0% with 4 of 67 patients experiencing BCAR of Banff grades IA, IB, IIA and

IIB. One of the four patients experiencing BCAR had a tacrolimus C_{min} of 3.0 ng/mL (below the recommended range) 2 days before the episode.[29]

Adult *De Novo* Liver Transplant Patients

Limited efficacy data for tacrolimus OD compared with standard tacrolimus, in *de novo* liver transplant recipients, are available from a randomised, nonblind, multicentre, pharmacokinetic study (see section 2), available as an abstract,[18] with additional data obtained from the EMEA scientific discussion.[21]

Liver transplant recipients aged 18–65 years with normal renal function and receiving the first dose of tacrolimus within 12–18 hours following skin closure were eligible for inclusion.[18] Excluded patients included those receiving organ transplants in addition to liver, an ABO incompatible donor liver or split donor liver or requiring antibody induction therapy.[18] Patients received tacrolimus OD (n = 67) or twice-daily standard tacrolimus (n = 62)[21] at an initial dosage of 0.10–0.15 mg/kg/day with target whole-blood C_{min} values of 10–20 ng/mL.[18] Patients also received corticosteroids.[21]

- The incidence of BCAR was 27% for both the tacrolimus OD group (18 of 67 patients) and the standard tacrolimus group (17 of 62 patients) after 6 weeks of treatment.[21] Kaplan-Meier estimates for patient and graft survival were 98.4% and 96.9% for the tacrolimus OD group and 98.1% and 93.3% for the standard tacrolimus group.[21]

Adult Stable Liver Transplant Patients

The efficacy of tacrolimus OD has been assessed in stable liver transplant recipients in a 2-year noncomparative study.[30] This followed an initial pharmacokinetic study in which patients were converted from twice-daily standard tacrolimus to tacrolimus OD (see section 2).[19]

Patients aged 18–65 years, ≥6 months post-liver transplant, taking stable doses of tacrolimus twice daily for ≥2 weeks with stable hepatic and renal function were eligible for inclusion into the initial pharmacokinetic study.[19] Excluded patients had received drugs known to interfere with tacrolimus metabolism, had a rejection episode within 90 days, or required antibody therapy for rejection within 6 months. Maintenance tacrolimus C_{min} values were 5–20 ng/mL. The mean patient age was 50.3 years.[19]

- After a treatment period of 2 years, 56 (81%) of the 69 patients who received at least one dose of tacrolimus OD remained in the study.[30] The mean tacrolimus OD dosage was 5.0 mg/day in 57 patients. Both patient and graft survival was 98.6% (68 of 69 patients), with 1 patient who had a functioning graft dying of squamous cell lung cancer. The incidence of BCAR was 5.8% with four patients experiencing BCAR of Banff grades I (two patients), II and III (one patient each); these responded to corticosteroid treatment.[30]

Paediatric Stable Liver Transplant Patients

A small pharmacokinetic and safety study provides limited efficacy data for tacrolimus OD in paediatric liver transplant patients converted from the same total daily dose of standard tacrolimus to tacrolimus OD.[20]

Enrolled patients were aged 5 to 13 years and ≥6 months post-liver transplant, receiving a standard tacrolimus twice-daily based immunosuppressant regimen that had been stable for ≥2 weeks, had tacrolimus whole-blood C_{min} values between 5 and 20 ng/mL, were able to swallow intact capsules, had not reached puberty and had a calculated creatinine clearance (Cr_{CL}) >50 mL/min/m^2.[20] Excluded patients had received sirolimus or drugs known to interfere with tacrolimus metabolism, had a rejection episode within 90 days or required antibody therapy for rejection within 6 months, had >2 rejection episodes in the last 12 months, abnormal liver function or an unstable medical condition.[20]

Throughout the study, tacrolimus target C_{min} values were 5–20 ng/mL, although lower concentrations were acceptable if there were no clinical indications to alter dose.[20]

- In the 18 patients who received at least one dose of tacrolimus OD, after 1 year of treatment, there

were no cases of acute rejection, graft loss, death or discontinuation of tacrolimus OD.[20]

4. Tolerability

The tolerability profile of standard tacrolimus is well established and has been reviewed previously.[1,8] The tolerability of tacrolimus OD and standard tacrolimus compared with ciclosporin has been assessed in *de novo* renal transplant recipients in a large, randomised, nonblind trial[13] (supplemented with data from the EMEA scientific discussion[21]) [see section 3]. Further information is available from pharmacokinetic studies,[17,19] with extended safety and efficacy follow-up after 2 years of treatment[29,30] in stable renal and liver transplant recipients converted from standard tacrolimus to tacrolimus OD, and from the manufacturer's prescribing information.[4] In paediatric patients, data following 1 year of treatment with tacrolimus OD are available from a pharmacokinetic and safety study.[20]

- The most common adverse reactions (frequency ≥10%) reported in the manufacturer's prescribing information for tacrolimus OD include tremor, headache, diarrhoea, nausea, renal impairment, hyperglycaemic conditions, diabetes, hyperkalaemia, hypertension and insomnia.[4] In addition, as with other immunosuppressants, patients receiving tacrolimus have an increased risk of infection and developing malignancies.[4] Increased susceptibility to infection and the possible development of lymphoma are included as black box warnings in the US prescribing information for standard tacrolimus.[6] Adverse reactions are often reversible and/or respond to dose reduction.[4]
- In the three-armed, randomised clinical trial, tacrolimus OD and standard tacrolimus were reported to have similar overall safety profiles; the differences in adverse event incidence observed between the standard tacrolimus group and the ciclosporin group were reported to be consistent with those previously reported.[13] Only key adverse events, rather than all adverse events, were reported.[13]
- Treatment-emergent adverse events with a significant difference in incidence, in patients receiving either tacrolimus OD or standard tacrolimus compared with those receiving ciclosporin, are illustrated in figure 2.[13] Adverse events led to discontinuation in 8.9% of the tacrolimus OD group, 10.8% of the standard tacrolimus group and 17.5% of the ciclosporin group.[13] Serious treatment-emergent adverse events considered to be related to the primary study drug were reported in 21.0% of the tacrolimus OD group, 23.1% of the standard tacrolimus group and 21.2% of the ciclosporin group; these led to discontinuation in 4.2%, 4.2% and 10.4% of each group, respectively.[21]
- In a *post hoc* analysis, adverse events with a difference in incidence ≥5% or significant difference in incidence between tacrolimus OD recipients and standard tacrolimus recipients were determined.[21] These included constipation (41.6% for the tacrolimus OD group vs 35.8% for the standard tacrolimus group), incision site complication (20.6% vs 28.3%), graft dysfunction (18.2% vs 23.6%), fatigue (15.9% vs 10.8%), urinary tract infection (15.9% vs 25.5%; $p = 0.0166$), cough (7.5% vs 12.7%), gastroenteritis (6.5% vs 0.5%; $p = 0.0008$), paraesthesia (5.6% vs 1.4%; $p = 0.0320$) and lower abdominal pain (4.7% vs 0.9%; $p = 0.0359$).[21]
- The incidence of bacterial, fungal or viral infections or adverse events reported as cytomegalovirus infection, cytomegalovirus viraemia or human polyomavirus infection was not significantly different between patients receiving tacrolimus OD or ciclosporin.[13]
- With the exception of TC (see section 1), there were no significant differences among groups in predefined clinically significant laboratory values.[13]
- After 1 year of treatment, mean Cr_{CL} was significantly higher in both the tacrolimus OD group and the standard tacrolimus group than in the ciclosporin group (3.52 vs 3.28 L/h; $p < 0.01$; and 3.46 vs 3.28 L/h; $p < 0.05$). However, there was no significant difference between groups in the incidence of serum creatinine levels ≥2.5 mg/dL (tacrolimus OD 0.6%, standard tacrolimus 2.1% and ciclosporin 1.7%).[13]

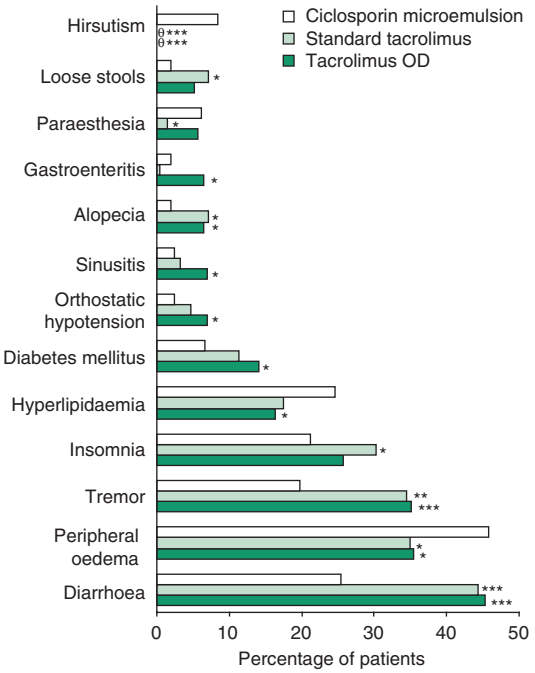

Fig. 2. Tolerability of tacrolimus once-daily (OD) formulation and twice-daily standard tacrolimus compared with twice-daily ciclosporin microemulsion. Treatment-emergent adverse events in a large (n = 638) randomised, nonblind, multicentre phase III trial with a statistically significant difference in incidence in patients receiving tacrolimus OD or standard tacrolimus compared with ciclosporin microemulsion. Patients were *de novo* renal transplant recipients and also received mycophenolate mofetil, corticosteroids and basiliximab induction.[13] θ indicates zero value; * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs ciclosporin microemulsion.

- After 2 years of treatment, mean Cr_{CL} was 3.48, 3.31 and 3.29 L/h in the tacrolimus OD, standard tacrolimus and ciclosporin groups, respectively (statistical analyses not reported).[14]

- After conversion to tacrolimus OD from standard tacrolimus, there was no increase in adverse events associated with tacrolimus use reported in the pharmacokinetic portion of studies in stable renal[17] and liver[19] transplant recipients. There were no new cases of post-transplant diabetes or glucose intolerance and serum creatinine levels remained stable. There were no changes in concomitant medications during this portion of the studies.[17,19]

- Following the pharmacokinetic portion of the conversion studies, only laboratory profiles, rejection episodes, serious adverse events and specific adverse events of interest were recorded.[29,30] In both studies, the investigators reported that the incidence of post-transplant diabetes, hyperlipidaemia, hypertension, infections, renal dysfunction and hepatic dysfunction were consistent with that observed historically with standard tacrolimus.[29,30]

- Laboratory results were reported by the investigators in both conversion studies to be unremarkable and stable in the 2 years of treatment postconversion.[29,30]

- During 2 years of treatment with tacrolimus OD following conversion in renal transplant recipients, 6 of 67 patients discontinued treatment because of adverse events and 1 of 67 patients discontinued because of calcineurin inhibitor toxicity.[29] Among serious adverse events experienced by >1 patient were cellulitis, acute renal failure (each occurring in 3 of 67 patients) human polyomavirus, pyelonephritis, urinary tract infection and increased creatinine blood level (each occurring in 2 of 67 patients).[29]

- In renal transplant patients during 2 years of treatment postconversion, there were no cases of new onset insulin or oral antihyperglycaemic agent use or of glycosylated haemoglobin ≥6%; however, new onset of a single fasting plasma glucose ≥126 mg/dL (≥6.99 mmol/L) was observed in 11 of 52 patients.[29]

- Throughout 2 years of treatment with tacrolimus OD in converted liver transplant recipients, 8 of 69 patients discontinued because of adverse events.[30] Among serious adverse events experienced by >1 patient were pyrexia, incisional hernia (each occurring in 4 of 69 patients), cholangitis, cholestasis, diarrhoea, influenza and pneumonia (each occurring in 2 of 69 patients).[30]

- In the same trial, new onset of a fasting plasma glucose level ≥126 mg/dL (≥6.99 mmol/L) was reported in 10 of 43 patients, new onset insulin use in 2 of 43 and new onset oral antihyperglycaemic use in 2 of 43. Significantly more patients who received prednisone developed a glucose abnormality than those that did not ($p = 0.0179$).[30]

- In paediatric stable liver transplant patients,[20] the safety profile of tacrolimus OD during the 1 year postconversion period was reported by the investi-

gators to be consistent with the known profile for standard tacrolimus. The majority of reported adverse events were mild to moderate and no patient discontinued because of an adverse event. Of the selected adverse events reported, all occurred in only one patient except vomiting which occurred in two patients. Laboratory results were reported by the investigators to be unremarkable and stable.[20]

5. Dosage and Administration

Tacrolimus OD should be administered in the morning with fluid (preferably water).[4] In order to achieve maximal absorption, capsules should be taken on an empty stomach or ≥1 hour before or 2–3 hours after a meal.[4]

In *de novo* renal transplant recipients, the initial dosage for the prophylaxis of transplant rejection is 0.20–0.30 mg/kg/day commenced within 24 hours of the completion of surgery.[4]

In *de novo* liver transplant recipients, the initial dosage for the prophylaxis of transplant rejection is 0.10–0.20 mg/kg/day commenced ≈12–18 hours after the completion of surgery.[4]

Patients maintained on standard tacrolimus twice daily can be converted to the same total daily dose of tacrolimus OD.[4]

Aided by whole-blood tacrolimus C_{min} monitoring (drawn ≈24 hours after last dose, just prior to next dose) [see Therapeutic Drug Monitoring in section 2], clinical assessments of rejection and tolerability in each individual should primarily form the basis of dosing.[4] In clinical practice, early in the post-transplant period, whole-blood C_{min} values are generally in the range of 10–20 ng/mL in renal transplant recipients and 5–20 ng/mL in liver transplant recipients. Blood concentrations are generally in the range of 5–15 ng/mL in renal and liver transplant recipients during subsequent maintenance therapy.[4]

Tacrolimus OD is not approved for paediatric patients.[4] While no dosage adjustment is required in renal impairment, careful monitoring of renal function is recommended because of the nephrotoxic potential of tacrolimus. Patients with severe liver impairment may require dosage reduction.[4]

Local prescribing information should be consulted for detailed information, including monitoring recommendations, contraindications, warnings, precautions, serious adverse reactions, potential drug interactions and use in special patient populations.[4]

6. Current Status: Tacrolimus Once-Daily Formulation

Tacrolimus OD has been approved in the EU[31] and is in preregistration in Japan and the US.[32] In the EU, tacrolimus OD is approved for the prophylaxis of renal or liver transplant rejection in adults and treatment of allograft rejection resistant to treatment with other immunosuppressants in adults.[4]

Phase III trials are planned or ongoing to further characterise the efficacy and safety of tacrolimus OD.[33]

The noninferiority of tacrolimus OD compared with ciclosporin, when each was used in conjunction with corticosteroids, mycophenolate mofetil and basiliximab induction, in *de novo* renal transplant patients has been demonstrated in a large, randomised, nonblind, multicentre trial. Smaller, randomised pharmacokinetic studies have provided data indicating similar efficacy and tolerability of tacrolimus OD to standard tacrolimus in *de novo* renal and liver transplant patients. Data after 2 years of treatment with tacrolimus OD have demonstrated the tolerability and efficacy of conversion from standard tacrolimus in stable renal and liver transplant patients.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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