Introduction

Tacrolimus extended-release capsules (TXR) were approved in the US by the Food and Drug Administration (FDA) in July 2013. The development of this new formulation garnered interest due to a possible improvement in immunosuppressive medication compliance. This formulation has been approved for use in European countries since 2007 under the trade name Advagraf®, as well as being approved for use in 73 countries worldwide.

Pharmacokinetics\(^1\)\(^{-25}\)

Studies in Normal Volunteers: There have been five Phase I pharmacokinetic trials published. These trials include both single dose and multiple dose crossover models. The studies demonstrated a delayed time to maximum concentration and a reduced \(C_{\text{max}}\) with the TXR product, in addition to a comparable AUC for the TXR product. The healthy volunteer studies support the bioequivalence of the TXR product to immediate release tacrolimus (TIR).

Stable Transplant patients: Studies were designed with an assumption that a 1:1 dose conversion was appropriate to provide equivalent blood levels of TXR. Over fifteen studies in pediatric and adult patients have been published regarding conversion of TIR to TXR. The trials have included renal, liver and heart transplants. The four industry sponsored trials demonstrated the formulations to be bioequivalent, using the FDA guidance of an AUC range 80-125%. However, this finding was not duplicated in clinical trials in stable transplant patients. These trials demonstrated statistically significant decreases in \(C_{\text{max}}\), often requiring dose increases of 11-14% to maintain therapeutic blood levels. One trial conducted in heart transplant patients utilized a conversion ratio of 1:1.25, resulting in appropriate blood levels in 31% of patients with the remaining patients requiring further dose increases.

De Novo transplant patients: Studies in this patient group have demonstrated a wide intra and inter patient variability in \(C_{\text{max}}\) and AUC in de novo patients. These variable pharmacokinetic factors have not been linked to an increased rejection rate. Rather, the findings demonstrate strongly the need for frequent blood level monitoring so that doses of TXR can be adjusted as needed.

Clinical Efficacy

Induction with Basiliximab (data on file)

This study was a randomized, open-label trial of TXR (N=214) compared to TIR (N=212), of 12 months duration conducted primarily in the US. Patients were stratified by donor type (living or deceased) and transplant history (primary or retransplant). All patients received basiliximab induction and concomitant treatment with mycophenolate mofetil (MMF) and corticosteroids. The population was 17 to 77 years of age, the mean age was 48 years; 64% of the study population was male; 73% were Caucasian, 22% were African-American, 2% were Asian, and 3% were categorized as other races. Living donors provided 49% of the organs. The actual TXR starting dose (given any time up to Day 2 post-transplant) of was higher than TIR (0.15 mg/kg versus 0.1 mg/kg). Thereafter, to achieve comparable mean tacrolimus trough concentrations (C24), higher total mean daily doses of tacrolimus were required for TXR than TIR (on average, by 15%). The most frequent diseases leading to transplantation were balanced between the groups and included nephrosclerosis/hypertensive nephropathy, diabetic nephropathy, glomerulonephritis, and polycystic kidney disease. Premature discontinuation from treatment at the end of one year occurred in 14% of TXR patients and 16% of TIR patients, primarily due to adverse reactions.
No Induction (data on file)
Study 2 was a randomized, double-blind trial, (designed to remain double-blind until the last patient enrolled had completed 24 weeks on study treatment) of TXR (N = 331) compared to TIR (N = 336), of 12 months duration conducted outside the US. The patient treatment assignment remained blinded for 12 months for 96% of the patients participating in the trial. Patients with a high immunologic risk defined as a PRA grade > 50% in the previous 6 months and/or with a previous graft survival of less than 12 months due to immunologic reasons were excluded, as were recipients of donor kidneys with cold ischemia time > 30 hours, or donor kidneys from a non-heart-beating donor. All patients received concomitant treatment with MMF and corticosteroids without antibody induction. The population was 18 to 65 years of age; the mean age was 48 years; 63% of the study population was male; 82% were Caucasian, 5% were African-American, 2% were Asian, and 11% were categorized as other races. Living donors provided 27% of the organs. Premature discontinuation from treatment at the end of one year occurred in 24% of TXR patients and 19% of TIR patients, primarily due to adverse reactions.

Once-daily TXR was compared with the twice-a-day TIR and cyclosporine microemulsion (CsA), all administered in combination with mycophenolate mofetil (MMF), corticosteroids and basiliximab induction, in a phase 3, randomized (1:1:1), open-label trial in 638 de novo kidney transplant recipients. In combination with MMF and corticosteroids, XL had an efficacy profile comparable to TIR and CsA. TXR/MMF and TIR/MMF were statistically noninferior at 1-year postransplantation to CsA/MMF for the primary efficacy endpoint, efficacy failure (death, graft loss, biopsy-confirmed acute rejection (BCAR) or lost to follow-up). One-year patient and graft survival were 98.6% and 96.7% in the XL/MMF group, 95.7% and 92.9% in TIR/MMF group and 97.6% and 95.7% in CsA/MMF group. The safety profile of TXR in comparison with CsA was similar to that observed with TIR in this study and consistent with previously published reports of TAC in comparison with CsA. The results support the safety and efficacy of tacrolimus in combination with MMF, corticosteroids and basiliximab induction, as well as TXR as a safe and effective once-daily dosing alternative.

There has been a 4-year follow-up report, on the above study. Patients receiving TXR and TIR showed comparable efficacy and safety profiles, with a higher incidence of new-onset diabetes after transplantation but superior renal function compared to patients receiving CsA.

A systematic review of TXR versus TIR in kidney transplant recipients was conducted by Ho, et al. They reviewed six randomized controlled trials (N=2499) and 15 observational studies (N=2886). There were no significant differences in biopsy-proven acute rejection (two trials, n=109); patient survival (three trials, n=1156); and graft survival (three trials, n=1156) between the two formulations at 12 months. The mean trough levels among recipients who received TXR was at least 40% lower than patients who received TIR within the first 6 weeks after transplantation. The additional dose required to achieve therapeutic targets among those who received TXR varied between 10% from trial data and 25% from observational studies within the first month after transplantation. Once again this demonstrates the need for therapeutic drug monitoring of TXR in transplant patients, including early and maintenance immunosuppression protocols.

There have been additional studies in liver transplant recipients converted from TIR to TXR. Gianelli et al reported on 65 patients with a median time since transplant of 39 months (range 6-83 months). Liver function, glucose and plasma lipid concentrations and arterial blood pressure remained stable during the study. Renal function improved during the 24 months of follow-up. No adverse events or acute rejection episodes were recorded during the study.

In a study of 125 stable liver transplant converted from TIR to TXR, renal and cardiovascular risk factors remained stable and no rejection episodes occurred over 12 months. It was noted that mean tacrolimus trough level concentration was 6.1 ± 2.3 ng/mL at study entry, decreased to 5.5 ± 2.1 ng/mL (P = 0.016) and 5.5 ± 2.2 ng/mL (P = 0.019) after 1 and 2 weeks on TXR, respectively, and tended to equal the baseline value during further follow-up. At week 1, tacrolimus concentrations were lower in 62.4% of patients and higher in 36.0% when compared with baseline.

A retrospective, observational, single-center study included 394 liver transplant patients with at least 6 months' postransplant follow-up and no rejection episodes in the last 3 months. The conversion from a TIR to TXR was done utilizing a 1:1 conversion ratio. The mean serum tacrolimus trough level decreased after conversion (6.1 ± 5.6 ng/mL before conversion versus 4.9 ± 2.5 ng/mL after conversion, P < 0.05). After a mean follow-up of 24 months after conversion, 6 patients had converted to cyclosporine, 14 patients had stopped calcineurin inhibitors, and 16 patients had returned to TIR, and 358 patients were still on TXR. Acute rejection episodes were observed in 7 patients.
Adherence

Maintaining medication adherence in the transplant population is crucial to the ability to have a functional graft. Adherence in this population can be compromised due to complex medication regimens with multiple daily doses and number of therapeutic agents as well as tolerance of these medication regimens. In a study which evaluated long-term patient adherence, as well as safety and efficacy, in stable patients after heart transplantation (HTx) who switched from a conventional twice daily calcineurin inhibitor-based regimen (TIR or cyclosporine A) to a once-daily TXR regimen. Adherence was measured using the Basel Assessment of Adherence with Immunosuppressive Medication Scale (BAASIS). Overall non-adherence at baseline for any of the four BAASIS items was 75.0% versus 40.3% after 8 months (P<0.0001). After 8 months, adherence was improved in 41 patients (56.9%), unchanged in 27 (37.5%), and reduced in four patients (5.6%). The BAASIS visual analog scale score improved significantly from 87.0% ± 13.5% to 97.5% ± 5.7% (P<0.0001). No significant changes were observed for hematological, renal, or liver function parameters after 8 months (all P=not significant).

In a prospective cohort study, treatment was switched from TIR to TXR with a simultaneous change to a once-daily formulation of other drugs when applicable. Treatment satisfaction was measured in 75 participants with the validated Treatment Satisfaction Questionnaire for Medication version II. The treatment convenience score increased from a mean (SD) of 66.0 (14.5) to 78.5 (14.5) (P < 0.001). The mean (SD) daily number of medication ingestion time points diminished from 2.4 (0.7) to 1.6 (0.7) (P < 0.001), and the mean (SD) daily number of tablets decreased from 12.4 (3.3) to 9.1 (2.6) (P <0.001). The self-reported adherence to the medication regimen increased from 79.7% to 94.6% (P < 0.001).

These same benefits on adherence have been demonstrated in smaller case series of less than 25 patients and will not be reviewed here.

Safety
Refer to the manufacturer's prescribing information for complete safety information.

Warnings and Precautions:

- Increased risk of infections and lymphoma, including latent virus activation (eg, BK virus-induced nephropathy)
- Risk of posttransplant diabetes mellitus, especially in black and Hispanic patients
- Black patients may require higher doses in kidney transplant
- Discontinue cyclosporine 24 hours before starting tacrolimus
- Combination immunosuppressant therapy
- Hypertension may occur; may treat with antihypertensives that are non-potassium-sparing diuretics
- Use caution with concurrent administration of nephrotoxic agents, calcium-channel blocking agents
- Mild-to-severe hyperkalemia may occur; avoid use of potassium sparing diuretics
- Myocardial hypertrophy reported (reversible with dose reduction or discontinuation)
- QT prolongation reported
- Use with strong CYP3A inhibitors and inducers: Adjust tacrolimus dose and monitor trough concentrations and for occurrence of adverse reactions, including QT prolongation
- Cases of pure red-cell aplasia reported; if this is diagnosed, consider discontinuing tacrolimus
- Gastrointestinal perforation; all reported cases were considered a complication of transplant surgery or accompanied by infection, diverticulum, or malignant neoplasm

Deaths and Other Serious Adverse Events (Sentinel Events):

Higher Mortality Rate in Female Liver Transplant Recipients

In a liver transplant study, mortality at 12 months was higher among female patients treated with TXR compared to female patients treated with TIR. Use in liver transplantation is not recommended.

Adverse Reactions:
The most common adverse drug reactions reported with TXR when dosed for immunosuppression in kidney transplant recipients included: diarrhea, constipation, nausea, peripheral edema, tremor, and anemia. The adverse effect profile of TXR is similar to that of TIR.

**Drug Interactions:**

Since tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes may increase tacrolimus whole blood concentrations. Drugs known to induce CYP3A enzymes may decrease tacrolimus whole blood concentrations. TXR should not be given with amphotericin b deoxycholate, cidofovir, mifepristone or oral neomycin.

When initiating therapy with voriconazole or posaconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be initially reduced to one-third of the original dose and the subsequent tacrolimus doses be adjusted based on the tacrolimus whole blood concentrations.

**Pregnancy and Nursing Mothers:** Pregnancy category: C

Lactation: Drug is excreted in breast milk; not recommended

**Dosage and Administration**

**TXR:**

Prophylaxis of organ rejection in patients receiving kidney transplants; used concomitantly with MMF and corticosteroids, with or without basiliximab induction

With basiliximab induction: MMF, corticosteroids, and initial tacrolimus dose may be administered before or within 48 hours after completion of renal transplantation but may be delayed until renal function has recovered 15 mg/kg PO once daily

Without induction: When agent is used with MMF and corticosteroids, preoperative dose should be given as single dose within 12 hours before reperfusion; initial postoperative dose should be given ≥4 hours after preoperative dose and ≤12 hours after reperfusion
Before operation: 0.1 mg/kg PO once daily
After operation: 0.2 mg/kg PO once daily

Postoperative oliguria: Initial postoperative dose should be administered ≥6 hours and ≤48 hours after transplantation but may be delayed until renal function shows evidence of recovery

With basiliximab induction: 0.15 mg/kg/day. When used with basiliximab induction, mycophenolate mofetil, and corticosteroids, the initial dose should be administered prior to or within 48 hours of the completion of the transplant procedure, but may be delayed until renal function has recovered.

Without induction: 0.1 mg/kg/day (preoperative); 0.2 mg/kg/day (postoperative). When used with mycophenolate mofetil and corticosteroids, the preoperative dose should be given as 1 dose within 12 hours prior to reperfusion; the initial postoperative dose should be given not less than 4 hours after the preoperative dose and within 12 hours after reperfusion.

**Conversion:**

Kidney transplant: When converting from immediate-release to extended-release (ER) therapy, initiate ER treatment in a 1:1 ratio (mg:mg) using previously established total daily dose of immediate release. Administer once daily.

**Missed dose:**

If a dose is missed, the dose may be taken up to 14 hours after the scheduled time (ie, for a missed 8:00 AM dose, take by 10:00 PM). Beyond the 14-hour time frame, wait until the usual scheduled time the following morning to take the next regular daily dose. Do not double the dose to make up for the missed dose.
Trough level, TXR with basiliximab induction (days 1-60): 5-17 ng/mL
Trough level, TXR with basiliximab induction (months 3-12): 4-12 ng/mL
Trough level, TXR without induction (days 1-60): 6-20 ng/mL
Trough level, TXR without induction (months 3-12): 6-14 ng/mL

**Budget Impact**

The effect of TIR to TXR conversion was analyzed by a budget impact model constructed from UK-specific data on acute rejection, graft failure, and mortality. Conversion was done using a 1:1 mg:mg basis. The model assumed that 3.1% of patients on TXR had high tacrolimus trough concentration variability compared with 17.4% on TIR, based on a study comparing pharmacokinetics of the two formulations. A relative graft failure risk of 2.38 was applied to high variability patients based on data from a tacrolimus variability study in which 10/148 patients with low variability experienced graft failure, compared with 24/149 in the high variability group. Mean per-patient cost (including tacrolimus, concomitant immunosuppressive medications, dialysis after graft failure, and treatment for acute rejection) was pound sterling (GBP) 26,941 (standard deviation [SD] = GBP 2765) with TXR vs GBP 30,356 (SD = GBP 3085) for TIR over a 5-year period, corresponding to a saving of GBP 3415 (SD = GBP 516) per patient or GBP 341,500 in a hypothetical 100-patient transplant center. Cost savings were driven primarily by lower dialysis costs resulting attributed to increased adherence with the TXR formulation and a lower proportion of TIR patients with high tacrolimus trough concentration variability (leading to lower graft failure risk).

**Acquisition Cost**

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<thead>
<tr>
<th>Astellas price per unit ($)</th>
<th>Mylan price per unit ($)</th>
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<tbody>
<tr>
<td>Tacrolimus extended release 0.5 mg</td>
<td>1.45</td>
</tr>
<tr>
<td>Tacrolimus extended release 1.0 mg</td>
<td>2.91</td>
</tr>
<tr>
<td>Tacrolimus extended release 5.0 mg</td>
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<tr>
<td>Tacrolimus twice daily 0.5 mg</td>
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<td>1.19*</td>
</tr>
<tr>
<td>Tacrolimus twice daily 5.0 mg</td>
<td>5.95*</td>
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*national contract prices current as of 7-8-14

**Conclusions**

The available pharmacokinetic data demonstrates potentially large inter and intra patient variability for tacrolimus. There appears to be some relation to the formulation type (TXR vs. TIR) however these results are not predictable or consistent. The pharmacokinetic studies of TXR in healthy volunteer, stable transplant and de novo transplant have demonstrated that a 1:1.25 conversion ratio may be needed to achieve equivalent C_max and AUC between the products. This is dependent on time post-transplant as well. It remains unclear if this variability in the pharmacokinetics of TXR are due to CYP3A5 polymorphisms, p-glycoprotein and/or other patient variables.

There are a multitude of observation, randomized/controlled, case series reports and open label pilot trials on the conversion from TIR to TXR. These studies involve most types of solid organ transplant; kidney, live, heart and lung. There was initial concern that an increase of biopsy-proven acute rejections with TXR, and there was speculation that this may be related to the lower peak concentrations. However, a recent meta-analysis of 6 randomized controlled trials and 15 observational studies found a non-significant difference in biopsy proven acute rejections and graft/patient survivals at 12 months between the two formulations. The overall findings of these studies is that conversion of TIR to TXR is safe and effective as long as appropriate TDM is provided, patients are educated about the conversion and that the same pharmaceutical manufacturer is utilized after conversion.

There is a new formulation of extended release tacrolimus, LCP-Tacro™ (Veloxis Pharmaceuticals, Hårsholm, Denmark), being developed for use in kidney (Phase III) and liver (Phase II) transplant recipients. LCP-tacrolimus has greater bioavailability than regular release tacrolimus, and only requires about 70% of the daily dose of regular release tacrolimus on average. The release of LCP-tacrolimus, which has small size particles of the drug embedded in the tablet being absorbed consistently over a full day, provides a time-to-concentration plot that is similar to that of a continuous infusion of intravenous tacrolimus, with significantly lower peak to trough variations. It will be interesting to see how this medication impacts transplant outcomes, safety, and medication compliance. 41, 42

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September 2014

Updated versions may be found at [www.pbm.va.gov](http://www.pbm.va.gov) or [http://vaww.pbm.va.gov](http://vaww.pbm.va.gov)
References

1. Astagraf (tacrolimus extended release): Astellas Northbrook, IL March 2014
2. First MR. First clinical experience with the new once-daily formulation of tacrolimus. Ther Drug Monit 2008 Apr; 30 (2): 159-66


