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MINIREVIEWS

Overview of extended release tacrolimus in solid organ transplantation

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Abstract

Tacrolimus (Prograf©, Astellas Pharma Europe Ltd, Staines, United Kingdom; referred to as tacrolimus-BID) is an immunosuppressive agent to prevent and treat allograft rejection in kidney transplant recipients in combination with mycophenolate mofetil, corticosteroids, with or without basiliximab induction. The drug has also been studied in liver, heart and lung transplant; however, these are currently off-label indications. An extended release tacrolimus formulation (Advagraf©, Astagraf XL©) allows for once-daily dosing, with the potential to improve adherence. Extended release tacrolimus has similar absorption, distribution, metabolism and excretion to tacrolimus-BID. Phase I pharmacokinetic trials comparing extended release tacrolimus and tacrolimus-BID have demonstrated a decreased maximum concentration (C_{max}) and delayed time to maximum concentration (t_{max}) with the extended release formulation; however, AUC_{0-24} was comparable between formulations. Overall extended release tacrolimus has a very similar safety and efficacy profile to tacrolimus-BID. It is not recommended in the use of liver transplant patient's due to the increased risk of mortality in female recipients. There has been minimal data regarding the use of extended release tacrolimus in heart and lung transplant recipients. With the current data available for all organ groups the extended release tacrolimus should be dosed in a 1:1 fashion, the exception may be the cystic fibrosis population where their initial dose may need to be higher.

Key words: Tacrolimus; Extended release tacrolimus; Pharmacokinetics; Pharmacoeconomics; Solid-organ transplant

Core tip: Tacrolimus is an immunosuppressive agent to prevent and treat allograft rejection in solid organ transplant recipients. An extended release tacrolimus formulation known as Astagraf XL is now available which allows for once-daily dosing, with the potential to improve adherence. Both tacrolimus formulations have demonstrated comparable steady-state systemic tacrolimus exposure in *de novo* kidney and liver transplant recipients. The following review will address the pharmacokinetics of extended release tacrolimus,

the data in solid-organ transplantation and the phamacoeconomic considerations of extended release tacrolimus compared to twice daily tacrolimus.

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INTRODUCTION

Tacrolimus (Prograf©, Astellas Pharma Europe Ltd, Staines, United Kingdom; referred to as tacrolimus-BID) is an immunosuppressive agent to prevent and treat allograft rejection in solid organ transplant recipients in combination with mycophenolate mofetil (MMF), corticosteroids, with or without basiliximab induction. The drug is currently only FDA approved for kidney transplant recipients. The drug has also been studied in liver, heart and lung transplant; however, these are currently off-label indications. An extended release tacrolimus formulation (Advagraf©, Astagraf XL©) allows for once-daily dosing, with the potential to improve adherence. Non-adherence with dosing has been a significant factor related to graft rejection and graft loss. Most patients receive immunosuppressants that require multiple doses a day. Patient compliance has been shown to be correlated with the number of prescribed medications taken daily; therefore, it is beneficial to simplify dosing frequency[1]. Both tacrolimus formulations have demonstrated comparable steady-state systemic tacrolimus exposure in *de novo* kidney and liver transplant recipients[2,3]. The following review will address the pharmacokinetics of extended release tacrolimus, the data in solid-organ transplantation and the phamacoeconomic considerations of extended release tacrolimus compared to tacrolimus-BID[2,3].

EXTENDED RELEASE TACROLIMUS PHARMACOKINETICS

Tacrolimus-BID is a calcineurin inhibitor which exerts its immunosuppressive effect through inhibition of interleukin-2 expression and subsequent T-lymphocyte activation[4,5]. It has variable oral absorption and is a substrate of P-glycoprotein with metabolism through cytochrome P4503A enzymes in the liver and small intestine. Studies have demonstrated differences in tacrolimus pharmacokinetics across various ethnic groups with higher doses needed in African American and Latin American recipients[6,7]. Therapeutic drug monitoring is essential to optimizing outcomes due to its variable bioavailability and narrow therapeutic index[8]. Trough concentrations (C_{min}) are the standard monitoring parameter due to its correlation with overall drug exposure (area under the curve from 0-24 h; AUC_{0-24}) and clinical efficacy.

Extended release tacrolimus is a modified release formulation, which utilizes ethylcellulose to prolong the drug release profile in the gastrointestinal tract *via* water permeation[9]. Extended release tacrolimus has similar absorption, distribution, metabolism and excretion to tacrolimus-BID. Phase Ⅰ pharmacokinetic trials comparing extended release tacrolimus and tacrolimus-BID have demonstrated a decreased maximum concentration (C_{max}) and delayed time to maximum concentration (t_{max}) with the extended release formulation; however, AUC_{0-24} was comparable between formulations (*P* values not available)[4,10,11]. The differences in C_{max} and t_{max} are consistent with a prolonged release formulation. Both formulations demonstrate a diurnal variation with approximately 35% reduction in AUC following the evening dose. Consequently, extended release tacrolimus should be administered in the morning on an empty stomach to optimize absorption. Similar therapeutic trough concentrations may be used for monitoring, as a high and equivalent correlation coefficient was reported between C_{min} and AUC_{0-24} for both formulations (*r* = not available)[4,10].

A 6 wk, phase Ⅱ, multicenter, open-label study compared the pharmacokinetics of extended release tacrolimus and tacrolimus-BID in *de novo* kidney transplant recipients on day 1, day 14, and 6 wk post-transplant (extended release tacrolimus *n* = 34; tacrolimus-BID *n* = 32)[12]. The AUC_{0-24} was approximately 30% lower for extended release tacrolimus on day 1; however, mean AUC_{0-24} was comparable on both day 14 and week 6 (Table 1). Trough concentrations were similar for both formulations by day 4. Similar reductions in initial AUC_{0-24} have been reported in *de novo* transplant recipients, which may necessitate an increased initial dose of extended release tacrolimus[3,12-15]. There was a strong correlation between AUC_{0-24} and C_{min} for extended release tacrolimus and tacrolimus-BID (r = 0.83 and r = 0.94, respectively; *P* = not available)[16].

A randomized, double-blind, phase Ⅲ trial was subsequently performed to study the effect of pre-transplant initiation of extended release tacrolimus and tacrolimus-BID on the pharmacokinetic profiles in *de novo* kidney transplant (extended release tacrolimus *n* = 17; tacrolimus-BID *n* = 17)[17]. The first dose of tacrolimus was administered within 12 h before reperfusion (day 0). The AUC_{0-24} was approximately 16% lower in the extended release tacrolimus group on day 1 (ratio of means 83.18%, 90%CI: 56.11%-110.25%), but reached comparable AUC_{0-24} to tacrolimus-BID on day 3 (ratio of means 102.2%, 90%CI: 76.21-128.18). The extended release tacrolimus group had a higher AUC_{0-24} compared to tacrolimus-BID on both day 7 (OR = 120.81%; 90%CI: 100.54-141.09) and day 14 post-transplant (OR = 121.24%; 90%CI: 104.29%-138.19%). Therefore,

Table 1 Comparison of pk parameters of tacrolimus administered as extended release tacrolimus and tacrolimus-BID[12]

PK parameter	Day 1		Day 14		Week 6	
	Extended release tacrolimus (n = 34)	Tacrolimus-BID (n = 32)	Extended release tacrolimus (n = 34)	Tacrolimus-BID (n = 32)	Extended release tacrolimus (n = 34)	Tacrolimus-BID (n = 32)
Mean (SD)						
AUC_{0-24} (ng · h/mL)	231.91 (102.33)	361.49 (214.65)	363.93 (96.61)	343.69 (105.83)	331.49 (86.82)	382.60 (171.22)
C_{max} (ng/mL)	18.24 (7.63)	34.16 (13.86)	29.87 (9.61)	31.74 (12.62)	26.38 (7.30)	33.04 (13.04)
C_{min} (ng/mL)	8.25 (5.01)	10.12 (6.98)	9.64 (3.25)	10.02 (3.04)	9.60 (2.93)	12.06 (5.91)
T_{max} (h)	4.4 (4.3)	1.7 (1.0)	2.4 (1.2)	1.6 (0.9)	2.4 (1.3)	1.9 (1.3)
Mean daily dose (mg/kg)	0.189	0.185	0.203	0.19	0.175	0.164

Table 2 Equivalence comparison of pharmacokinetic parameters after conversion tacrolimus-BID to extended release tacrolimus[19]

PK parameter	Extended release tacrolimus (n = 60)	Tacrolimus-BID (n = 60)	Ratio (90%CI) extended release tacrolimus: Tacrolimus-BID
AUC_{0-24} (ng · h/mL)	217.75	234.42	92.9% (89.9-96.0)
C_{max} (ng/mL)	15.99	21.84	73.2% (67.7-78.7)
C_{min} (ng/mL)	6.60	7.26	90.9% (87.3-94.6)

initiation of extended release tacrolimus prior to transplantation may minimize differences in exposure between formulations in the early post-transplant period. These data support the FDA-approved dosage recommendation for extended release tacrolimus in *de novo* renal transplantation (Table 1)[9]. Frequent monitoring of trough concentrations should be implemented in order to minimize excessive exposure as evidenced by supratherapeutic concentrations.

Two additional conversion studies from tacrolimus-BID to extended release tacrolimus have demonstrated similar steady-state pharmacokinetics between formulations after a milligram-for-milligram conversion in stable kidney transplant recipients[18,19]. Both studies used a single sequence, cross-over design with four pharmacokinetic evaluations at steady-state conditions (Table 2). These data support the conversion of tacrolimus-BID to extended release tacrolimus on a 1:1 (mg:mg) total daily dose basis. However, reductions in C_{min} and AUC_{0-24} have been reported following conversion in multiple studies in various solid-organ transplant populations with a dose escalation requirement in up to 50% of recipients[19-24]. Therefore, close therapeutic drug monitoring is warranted following conversion between formulations.

Regarding special populations, extended release tacrolimus is subject to the same renal and hepatic impairment recommendations as tacrolimus-BID. The mean clearance of tacrolimus in patients with renal dysfunction is similar to that in healthy subjects[3]. Tacrolimus is not dialyzed to any significant extent due to its poor aqueous solubility and extensive erythrocyte and plasma protein binding. Severe hepatic impairment (mean Child-Pugh score > 10) necessitates more frequent monitoring of tacrolimus C_{min} due to significant reduction in drug clearance and risk of accumulation. Pertinent pharmacokinetic considerations for non-renal transplant recipients are addressed in the organ-specific section.

KIDNEY TRANSPLANTATION

Extended release tacrolimus is currently only FDA approved for the prophylaxis of rejection in patients that have received a kidney transplant[9]. One study examined extended release tacrolimus/MMF, compared to tacrolimus-BID/MMF and cyclosporine (CsA)/MMF in *de novo* kidney transplant recipients. This was a phase 3, randomized, open-label, multicenter three-arm noninferiority trial (3 arms: Extended release tacrolimus/MMF n = 214; tacrolimus-BID/MMF n = 212; CsA/MMF n = 212)[2]. Included patients were ⩾ 12 years of age who received a primary or re-transplanted deceased donor or living donor renal transplant, and received the study drug within 48 h of the transplant. Overall 668 patients were randomized and 638 patients received at least one dose and were included in the efficacy and safety analyses. Mean total daily doses were similar between the tacrolimus-BID/MMF and extended release tacrolimus/MMF groups, however slightly more patients in the extended release tacrolimus/MMF group compared to the tacrolimus-BID/MMF group had trough concentrations below target but these differences were not significant and very minimal [above target day 3: Extended release tacrolimus compared to tacrolimus-BID 19% (n = 36), 27.3% (n = 47); month 2: 5.6% (n = 10), 6.7% (n = 11); month 4: 7.5% (n = 13), 4.6% (n = 7); below target day 3: Extended release tacrolimus compared to tacrolimus-BID 30.7% (n = 58), 27.9% (n = 48); month 2: 18.2% (n = 33), 10.15% (n = 17.6); month 4: 10.3% (n = 18), 13.2% (n = 20) respectively]. Efficacy rates in both tacrolimus groups were statistically non-inferior to that in the CsA group. Kaplan-Meier estimates for 1-year patient and graft survival (extended release tacrolimus/MMF 98.6%, 95%CI: -1.6%, 3.6% and 96.7%, 95%CI: -2.7%, 4.6%; tacrolimus-BID/MMF 95.7%, 95%CI: -5.3%, 1.5% and 92.9%, 95%CI: -7.3%, 1.6%; CsA/MMF 97.6% and 95.7%) were similar among the 3 groups.

Incidence of biopsy-proven acute rejection (BPAR) at 6 mo and 1 year was significantly lower in the tacrolimus-BID/MMF group compared to the CsA/MMF group; however, there was no statistical difference between the extended release tacrolimus/MMF and CsA/MMF group. Overall extended release tacrolimus/MMF was noninferior to CsA/MMF and has a similar efficacy and safety profile to tacrolimus-BID/MMF when combined with corticosteroids and basiliximab induction[2]. In 2014 Silva *et al*[25] published the 4-year follow-up results to the original study. Mean trough concentrations of extended release tacrolimus and tacrolimus-BID was similar starting at 1 year ranging from 6.5-7.5 ng/mL in extended release tacrolimus and 6.1-7.8 ng/mL in tacrolimus-BID. All groups had similar efficacy reflected by patient and graft survival. In the extended release tacrolimus, tacrolimus-BID, and CsA groups patient survival was 93.8% (95%CI: 90.5%, 97.2%), 93.2% (95%CI: 89.8%, 96.7%) and 92.5% (95%CI: 88.6%, 96.3%) respectively, while graft survival was 88.1% (95%CI: 83.7%, 92.6%), 85.4% (95%CI: 80.5%, 90.4%), and 85.3% (95%CI: 80.3%, 90.4%) respectively. There was a higher rate of graft failure amongst African Americans compared to Caucasians. Graft loss for extended tacrolimus was 11.9% (19/160) in Caucasians and 19.5% (8/41) in African Americans, for tacorlimus-BID it was 10.5% (16/153) in Caucasians and 31.4% (16/51) in African Americans, and for CsA 12.3% (20/163) in Caucasians and 22.2% (8/36) in African Americans but this is consistent with 5-year data from the Scientific Registry of Transplant Recipients[26]. Overall patient and graft survival rates were high and there was no statistically significant difference amongst groups. Of note this study included a relatively low-risk population and adherence was not evaluated[25].

In 2010 a phase Ⅲ multicenter, 1:1 randomized, parallel-group, noninferiority study that compared the efficacy and safety of tacrolimus-BID and extended release tacrolimus when combined with low dose MMF and corticosteroids without antibody induction in *de novo* kidney transplant recipients was published. The study included patients 18-65 years of age receiving a kidney transplant from a donor 5-65 years of age who were ABO compatible[3]. Patients were excluded if they had received a previous non-renal transplant, panel reactive antibody > 50%, cold ischemic time > 30 h, uncontrolled infection or malignancy. The initial post-operative dose was 0.2 mg/kg per day for both formulations; matching placebo was taken twice daily. Overall 667 patients were randomized (tacrolimus-BID n = 336; extended release tacrolimus n = 331). The mean daily dose of extended release tacrolimus was higher than tacrolimus-BID at all time points, however whole-blood trough levels were lower in the extended release tacrolimus group at week 1 (12.8 ± 4.8 ng/mL *vs* 15.3 ± 5.8 ng/mL, $P < 0.05$) but comparable thereafter[3]. This is consistent with findings from a previous phase Ⅱ *de novo* study that showed tacrolimus exposure was lower with extended release tacrolimus than tacrolimus-BID on day 1 but was similar by day 4[3,16,21]. At 24 wk the BPAR rate was 15.8% *vs* 20.4% in the tacrolimus-BID and extended release tacrolimus group (P = 0.182). There was no correlation with early trough levels and the incidence of BPAR. Kaplan-Meier survival rates were 98.8% for both arms at week 24 and 97.5% and 96.9% at 12 mo for tacrolimus-BID and extended release tacrolimus respectively. Graft survival rates were 94.6% and 93.6% at 24 wk and 92.8% and 91.5% at 12 mo respectively. The incidence of delayed graft function, serum creatinine (SrCr) and creatinine clearance did not differ significantly between the two groups at any time point of the study. Overall this study had similar efficacy and comparable safety profile with tacrolimus-BID and extended release tacrolimus in a regimen that used low dose MMF without antibody induction in *de novo* kidney recipients[3].

A multicenter, prospective, randomized extension study compared extended release tacrolimus to tacrolimus-BID beyond 6 mo to explore rejection, graft and patient survival[13]. The initial study was a phase Ⅲ, randomized, open-label, comparative, multicenter study in *de novo* living donor kidney transplant recipients[27]. The initial dose of extended release tacrolimus was 0.3 mg/kg daily or 0.15 mg/kg of tacrolimus-BID. The extension of the 6-mo *de novo* study was designed as a 39-mo, single-arm follow-up to evaluate the efficacy and safety of extended release tacrolimus. A total of 124 patients were randomized. The rate of BPAR was similar between groups [19.4% extended release tacrolimus group *vs* 16.1% in tacrolimus-BID (P = 0.638)]. Forty-four patients were enrolled in the 39-mo extension study. One patient in the extended release tacrolimus group experienced BPAR at 29 mo who was treated with pulse steroids and subsequently graft function recovered. During study period 4 recipients (9.1%) were converted back to BID dosing due to skin rash, elevated SrCr without evidence of rejection, study medication prohibited and BPAR. Overall, extended release tacrolimus was shown to be safe and effective for nonsensitized kidney transplant recipients[27].

Yang *et al*[28] performed a 24-wk prospective, single-center, open-label, randomized trial to evaluate the safety and efficacy of switching tacrolimus-BID to extended release tacrolimus in stable renal patients. Patients were included if they were > 20 years of age, had received a kidney transplant ⩾ 12 mo prior to enrollment and maintained a stable tacrolimus dose at least 12 wk before the start of the study drug. They were excluded if they had a prior organ transplant, acute rejection within the past 12 wk, malignancy after transplant, focal segmental glomerulosclerosis and SrCr > 1.6 mg/dL. Patients were randomized to either tacrolimus-BID or extended release tacrolimus and doses were converted on a 1:1 (mg:mg) basis to determine to total daily dose. Ninety-nine patients

were randomized, 50 in the tacrolimus-BID group and 49 in the extended release tacrolimus group. There were no deaths or graft losses during the study period. Two patients in the extended release tacrolimus group (4.5%) experienced acute rejection and were treated with high dose steroids and their renal function recovered. There was no significant difference in the incidence of acute rejection at week 24 between the 2 groups[28]. Initially tacrolimus whole-blood concentrations were significantly lower in the extended release tacrolimus group, however were still in the therapeutic range. This is once again consistent with previous pharmacokinetic studies that showed slower absorption of extended release tacrolimus compared to tacrolimus-BID[29,30]. The rate of compliance was 99.4% in the tacrolimus-BID group and 99.6% in the extended release tacrolimus group. The similarity in compliance amongst groups could be attributed to the small study population and short-term follow-up. Overall the extended release formulation can be considered as an effective alternative to current tacrolimus formulations in stable renal transplant recipients[28].

The OSAKA trial was a phase Ⅲ trial that evaluated the non-inferiority of extended release tacrolimus *vs* tacrolimus-BID in kidney transplantation[31]. This was one of the largest randomized clinical trials that was conducted in kidney transplant recipients. Patients were randomized to 1 of 4 groups: Tacrolimus-BID 0.2 mg/kg per day (arm 1); extended release tacrolimus 0.2 mg/kg per day (arm 2); extended release tacrolimus 0.3 mg/kg per day (arm 3); extended release tacrolimus 0.2 mg/kg per day + basiliximab + corticosteroid bolus (arm 4) and 1214 patients received at least one dose of study drug. Extended release tacrolimus 0.3 mg/kg per day had higher trough concentrations on day 1 and 7 however, by day 14 they were similar across the board. Non-inferiority was established for efficacy failure rates between arms 1 and 2. Non-inferiority of efficacy failure between arm 3 and 1 was not established, nor was it between arms 4 and 1. The main reason for efficacy failure in all arms was graft dysfunction at week 24. The number of patients that experienced BPAR was 13.6% (42/309) in arm 1, 10.3% (31/302) in arm 2, 16.1% (49/304) in arm 3, and 12.7% (36/283) in arm 4. Overall, the efficacy of extended release tacrolimus dosing of 0.2 mg/kg per day was non-inferior to tacrolimus-BID dosing based on the same initial dosing without induction. Increasing the starting dose to 0.3 mg/kg per day did not increase efficacy; therefore, 0.2 mg/kg per day was and adequate starting dose[31].

LIVER TRANSPLANTATION

There are several studies evaluating the pharmacokinetics, safety, and efficacy of extended release tacrolimus in liver transplant recipients. However, extended release tacrolimus is currently not FDA-approved for use in the liver transplant setting due to an increased mortality rate in female liver transplant recipients in a *post-hoc* analysis[9].

The first long-term liver transplant trial with extended release tacrolimus was a multicenter, randomized, double-blind, phase Ⅲ study comparing the efficacy and safety of extended release tacrolimus to tacrolimus-BID[13]. The duration of the study was 24 wk followed by an extension period to 12 mo post-transplant. The extended release tacrolimus arm (n = 237) received initial dose of 0.2 mg/kg per day, while the tacrolimus-BID (n = 234) received 0.05 mg/kg per dose given twice daily. The extended release tacrolimus arm was given a higher initial dose due to lower tacrolimus levels seen in the first few days post-transplant in a previous pharmacokinetic study[19]. Both groups were subsequently adjusted to maintain goal trough concentrations. The primary endpoint was the rate of BPAR within 24 wk post-transplant, with an incidence of 36.3% in the extended release tacrolimus group and 33.7% in the tacrolimus-BID group (P = 0.512)[13]. Furthermore, at 12 mo the extended release tacrolimus group and tacrolimus-BID group had a similar patient survival rate (89.2% and 90.8%, respectively P = 0.535) and graft survival rate (85.3% and 85.6%, respectively P = 0.876). There were no clinically relevant differences in the causes of death between the two treatment groups. In a *post-hoc* analysis, a higher mortality rate was observed in the female recipients compared with the male recipients receiving extended release tacrolimus (18.4% *vs* 6.8%, P = 0.026). There is currently no explanation for this difference in mortality. Consequently, extended release tacrolimus is not approved for use in liver transplant recipients.

The DIAMOND Study is a multicenter, 24-wk, randomized, open-label trial studying the effects of different extended release tacrolimus dosing regimens on renal function in *de novo* liver transplant recipients[32]. There were 3 treatment arms: Arm 1 (extended release tacrolimus 0.2 mg/kg per day, n = 295), arm 2 (extended release tacrolimus 0.15-0.175 mg/kg per day + basiliximab, n = 286), or arm 3 (extended release tacrolimus 0.2 mg/kg per day delayed until Day 5 + basiliximab, n = 276). Estimated glomerular filtration rate (eGFR) using the four-variable Modified Diet in Renal Disease equation was significantly higher in arms 2 and 3 compared to arm 1 (P = 0.001 and P = 0.047, respectively). Additionally, there was significantly less BPAR in arm 2 compared to arms 1 and 3 (P = 0.016, P = 0.039, respectively). Overall, there were similar estimates of composite failure-free survival in arms 1-3 (72.0%, 77.6%, 73.9%, respectively, P = 0.065, P = 0.726, P = 0.161) and no significant difference in mortality between males and females receiving extended release tacrolimus.

A retrospective analysis of the European Liver Transplant Registry was performed to investigate long-term outcomes with extended release tacrolimus compared to tacrolimus-BID (extended release tacrolimus n = 528, tacrolimus-BID n = 3839)[33]. Propensity

score-matched analyses were performed to minimize bias associated with differences in donor and recipient baseline characteristics. The registry data showed a significant improvement in patient and allograft survival over 3 years in patients receiving extended release tacrolimus (P = 0.004 and P = 0.001, respectively). Given the limitations of registry analysis, additional studies are needed to further validate these long-term findings.

Several prospective, observational studies have investigated the safety and efficacy of conversion from extended release tacrolimus to tacrolimus-BID in stable liver transplant recipients[21,33-35]. All studies have shown comparable patient and allograft survival with no difference in incidence of BPAR or adverse effects. Beckebaum *et al*[34] also found a statistically significant reduction in nonadherence from 66% at study entry to 30.9% at 12 mo post-conversion from tacrolimus-BID to extended release tacrolimus using the "Basel Assessment of Adherence Scale to Immunosuppressives" (P < 0.001). The improved adherence to immunosuppression and decreased intra-subject variability in drug exposure may potentially translate into improved long-term patient and allograft survival.

Regarding extended release tacrolimus pharmacokinetics in the liver transplant population, once daily dosing has an overall similar systemic exposure as compared to the standard tacrolimus-BID regimen[9,21,34-37]. Given the strong correlation between $AUC_{0\text{-}24}$ and trough concentrations for extended release tacrolimus, the same therapeutic monitoring and target trough concentration range can be used for both formulations.

However, in the *de novo* liver transplant setting, systemic exposure ($AUC_{0\text{-}24}$) was 50% lower in extended release tacrolimus compared to equivalent doses of tacrolimus-BID. Similar trough levels between the two formulations were obtained by day 4 after implementation of dose adjustments. Consequently, initial doses for extended release tacrolimus may need to be slightly higher than tacrolimus-BID to achieve similar tacrolimus trough blood concentrations in *de novo* liver transplant recipients. The pharmacokinetic studies in stable liver transplant recipients have demonstrated a safe 1:1 daily dose conversion from tacrolimus-BID to extended release tacrolimus with close monitoring of trough concentrations[21,34,35].

In summary, extended release tacrolimus has proven to be well tolerated with a similar safety and efficacy profile as compared to tacrolimus-BID. Extended release tacrolimus is not FDA approved for use in liver transplant recipients due to increased mortality rate in females in a *post-hoc* analysis. While the increased mortality is a concern, this finding has not been replicated in follow-up clinical trials or registry data. Extended-release tacrolimus may be particularly beneficial in improving immunosuppression compliance and subsequently long-term outcomes in the liver transplant population, as many recipients are maintained on tacrolimus monotherapy.

HEART TRANSPLANTATION

Limited published data exists investigating the use of extended release tacrolimus in both *de novo* and established patients with heart transplants. Therefore, extended release tacrolimus is not approved for the prophylaxis of rejection in heart transplant patients in the United States or Europe[9].

A phase Ⅱ pharmacokinetic study was performed in patients that were at least 6 mo post heart transplant and were receiving tacrolimus-BID with stable levels between 5-15 ng/mL. Patients continued tacrolimus-BID study days 1-7 and were transitioned to extended release tacrolimus at 1:1 mg/d for days 8-35 of the study. Of the 85 patients enrolled, only 45 patients had complete 24 h pharmacokinetic data collected in the tacrolimus-BID and extended release tacrolimus phase necessary for analysis. The primary endpoint of the study was the comparison of the systemic exposure ($AUC_{0\text{-}24}$) at steady state of tacrolimus-BID to extended release tacrolimus, with a predefined acceptance range for a 90%CI of 80%-125%. The $AUC_{0\text{-}24}$ was 219.77 ng·h/mL for extended release tacrolimus compared to 242.86 ng·h/mL for tacrolimus-BID, with a 90%CI of 86.4%-94.6%, falling within the predefined acceptable range. The $AUC_{0\text{-}24}$ and C_{min} correlated well for both tacrolimus XL (r = 0.94) and tacrolimus BID (r = 0.91). During the study, 32.9% of the overall patients enrolled needed a dose adjustment after conversion to extended release tacrolimus. A dose increase was needed in 25.9% of patients, and 6.2% of patients required a dose decrease. No adverse events led to discontinuation during the study, and there were no reports of acute rejection, graft loss, or death. This pharmacokinetic evaluation suggests that overall exposure to tacrolimus is lower with the extended release product, with comparable correlation between trough levels and $AUC_{0\text{-}24}$ as with tacrolimus-BID[22].

Patients enrolled in the phase Ⅱ pharmacokinetic study were given the option of continuing extended release tacrolimus in a long-term extension study. Of the 85 patients enrolled in the pharmacokinetic study, 79 patients chose to take part in the extension study that included heart, kidney, and liver transplant patients. The primary endpoint of the study was patient and graft survival, with the secondary endpoints of BPAR and safety events. Survival at four years was 92.5% in the heart transplant arm, with graft survival rate being 92.2%. Patients free from BPAR were 87% at four years. The primary reasons for study withdrawal were withdrawn consent or non-adherence to study schedule. Renal function as reflected by mean serum creatinine and creatinine clearance rates were stable across the four year study. Authors concluded that the adverse event rates seen in the study were similar to that of reported rates with tacrolimus-BID, suggesting

that extended release tacrolimus may be considered an alternative to conventionally dosed tacrolimus[36].

As previously discussed in the article, package insert data for extended release tacrolimus suggests that patients be converted to the once daily product from tacrolimus-BID in a 1:1 ratio based on total mg/d dosing. A study of 75 heart transplant recipients were converted to extended release tacrolimus at a 25% increased dose from the tacrolimus-BID total daily dose. The retrospective analysis followed patients for 3 mo and included patients that were 61.7 ± 48.5 mo from transplant, with therapeutic troughs defined as 10-15 ng/mL within the first year following heart transplant, and 5-15 ng/mL thereafter. Two of the 75 patients (2.7%) failed to achieve therapeutic levels despite dose increases, and therefore discontinued extended release tacrolimus. Twenty-three patients (31%) required no dose adjustment following conversion, and 51 patients (68%) required one or two dose adjustments. Three patients experienced BPAR during the study period without hemodynamic compromise. Although the authors state that there were no differences in reports of glycemic control, serum creatinine, lipids, or blood pressure from pre-conversion values, these rates and values are not included in the publication. This suggests an alternative approach to conversion from conventionally dosed tacrolimus-BID to extended release tacrolimus in heart transplant recipients. The need for close monitoring of trough levels following conversion is also highlighted as 2.7% of patients were unable to achieve therapeutic levels[38].

More recently, two studies evaluated the use of extended release tacrolimus in comparison to tacrolimus-BID in *de novo* heart transplant patients. The first followed 11 patients converted to extended release tacrolimus on post-operative day 14 from CsA, with an initial extended release tacrolimus dose of 6 mg/d. These patients were case matched to 11 patients managed with tacrolimus BID at an initial dose of 3 mg-BID. Target tacrolimus troughs in both groups were 5-8 ng/mL. Patients were followed for 36 mo with a primary composite endpoint of death, graft loss, and drug discontinuation, which occurred less often in the extended release tacrolimus arm (18.2% *vs* 45.54%, $P = 0.277$). Survival at three years was greater for extended release tacrolimus (90% *vs* 77.9%, $P = 0.291$) and more patients remained on the prescribed therapy in the extended release tacrolimus arm (90.9% *vs* 77.9%, $P = 0.533$). The occurrence of secondary endpoints including BPAR, malignancy, infection, and safety events did not differ between groups. The total daily dose required to achieve therapeutic trough levels was higher in the extended release tacrolimus arm (numeric values not reported). Although the safety and efficacy from this small study suggest the feasibility of extended release tacrolimus in *de novo* heart transplant recipients, the dosing strategies used to manage these patients in order to achieve therapeutic trough levels may require further investigation[39].

The second study evaluating extended release tacrolimus in *de novo* heart transplants randomized 19 patients, 8 to open label extended release tacrolimus and 11 to open label tacrolimus-BID. Both groups started the calcineurin inhibitor therapy on post-operative day four. Patients in the extended release tacrolimus group received initial doses of 0.5 mg/20 kg per day, with tacrolimus-BID patients receiving 0.5 mg/20 kg per dose, dosed twice daily. Initial trough targets were 8-15 ng/mL. Patients were followed for an average of 290 ± 92 d for BPAR, incidence of renal insufficiency, new hypertension, and new onset diabetes. There were no differences between the two groups for any staging of rejection throughout the follow-up period. Although total daily doses between the extended release tacrolimus group and the tacrolimus-BID group did not differ at eight and thirty days, the total daily dose of extended release tacrolimus was significantly lower than tacrolimus-BID at six months (3 ± 1 mg/d *vs* 6 ± 2 mg/d, $P < 0.05$). There was no difference between groups in the rate of treated hypertension or diabetes. Although a low number of patients were included in this study, this prospective analysis suggests that patients managed with extended release tacrolimus for *de novo* heart transplant may have similar efficacy and safety outcomes[40].

The published data supporting the use of extended release tacrolimus in heart transplant recipients is limited, yet current evidence does not signal that the therapy is associated with worse efficacy or safety outcomes when compared to tacrolimus-BID. Additionally, a small study of 72 patients suggests that use of extended release tacrolimus as compared to previous regimens of tacrolimus-BID or CsA decreased rates of patient reported non-adherence measures at eight months[41]. Further studies evaluating the use of extended release tacrolimus in heart transplant recipients is needed to define the role of the extended release product in this patient population.

LUNG TRANSPLANTATION

To date, only 2 studies evaluating extended release tacrolimus have been performed in lung transplant recipients. The studies are not outcomes based, only pharmacokinetic in nature assessing the potential for use in stable lung transplant recipients. Therefore, extended release tacrolimus is not FDA approved for the use in *de novo* lung transplantation[9].

The first study evaluated the conversion of tacrolimus-BID to extended release tacrolimus in 19 stable lung transplant recipients. This was a phase Ⅱ, open-label, single center, single arm, prospective trial. The primary outcome was a pharmacokinetic comparison of tacrolimus-BID to extended release tacrolimus on a 1:1 basis through analyzing $AUC_{0\text{-}24}$ on

both dosing regimens. Secondarily, episodes of acute cellular rejection (ACR) at 6 mo and any other adverse events throughout the trial period were assessed. All patients were at least 180 d post transplantation and had stable trough levels of tacrolimus-BID ranging from 5-15 ng/mL upon entering the study. Notably, patients with cystic fibrosis (CF) or with ongoing ACR, recent ACR, or chronic rejection were excluded. All patients were receiving tacrolimus, an antimetabolite (MMF or azathioprine), and corticosteroids[31]. Patients were converted on a 1:1 (mg:mg) basis from tacrolimus-BID to extended release tacrolimus after being stable for 30 d on tacrolimus-BID. Doses were adjusted as needed on extended release tacrolimus to maintain the previous goal concentrations of 5-15 ng/mL. Two 24 h PK curves were created: one on tacrolimus-BID and the other on extended release tacrolimus. The AUC_{0-24}, C_{min}, and T_{max} were then compared[42].

The results of this trial demonstrated the mean AUC_{0-24} (SD) of tacrolimus-BID was 279.8 (57.7) ng/mL per hour compared to 278.7 (52.5) ng/mL per hour for extended release tacrolimus (P = 0.92). No statistically significant differences were noted between the $C_{max0-24}$ and $C_{min0-24}$. The time to maximum concentrations did differ between tacrolimus-BID and extended release tacrolimus, 1.5 h *vs* 3 h, respectively. The AUC_{0-24} and C_{min} correlated well for both products. It was noted that the mean tacrolimus-BID dose (before switching) was 4.8 ± 2.2 mg. After switching to extended release tacrolimus, the mean dose increased to 5.2 ± 2.6 on day 60, 5.4 ± 3.0 mg on day 90, and 5.6 ± 3.1 on day 180[42].

After 6 mo, 8 patients were on the same total dose, 4 patients required a 1 mg reduction, 4 patients required a 1 mg increase, and 3 patients required more than a 1 mg increase. Throughout the study period, 4 severe adverse events occurred (lithiasic pyelonephritis, urinary sepsis, acute cholecystitis, stroke). These were not considered related to extended release tacrolimus. There were no episodes of ACR. This trial demonstrated that converting patients from tacrolimus-BID to extended release tacrolimus on a 1:1 basis provides virtually identical drug exposure when analyzed by the AUC_{0-24} in the lung transplant population; however, long term outcomes are lacking[42].

The second trial was a pharmacokinetic study. However, it included only patients with CF, who were notably excluded in the previous trial. Overall, 12 adult CF patients (7 men, 5 women) were enrolled. All patients were on a stable dose of tacrolimus BID upon entering the trial for at least 4 wk. After conversion to extended release tacrolimus on a 1:1 basis, doses were once again titrated to achieve a therapeutic trough of 10-15 ng/mL[43].

Nine (82%) of the patients required a significant dose adjustment after conversion to extended release tacrolimus. Percentage increases ranged from 28%-66.7%. The mean (SD) daily dose of tacrolimus-BID upon enrollment was 0.17 (0.10) mg/kg per day and this increased to 0.22 (0.12) mg/kg per day after switching to extended release tacrolimus. The mean (SD) AUC_{0-24} for tacrolimus BID was 414.28 (159.43) ng • h/mL *vs* 388.88 (104.05) ng • h/mL for extended release tacrolimus after switching[32]. During the study and follow up no episodes of ACR were noted. This trial demonstrated that extended release tacrolimus is a possible alternative in CF patients, however, on average they need a 28% increase in dose and the range of the increase can be up to 67%. This is in contrast with the previous study of non-CF lung transplant recipients who can safely be converted on a 1:1 basis. Long term data is still needed in CF as well with extended release tacrolimus[43].

PHARMACOKINETIC CONSIDERATION

The effect of medication adherence to immunosuppressive therapies on risk of acute rejection and graft loss is well documented and has significant impact on graft survival[44]. A 2004 meta-analysis evaluated the frequency of and effect of immunosuppressive non-adherence in renal transplant recipients and found non-adherent patients were 7.1 times more likely to experience graft failure than adherent patients[34]. The most common types of nonadherence seen in the meta-analysis was missing, forgetting, or altering a dose at least once per month. A 2012 study conducted in France demonstrated an inverse relationship between the number of immunosuppressant medications and the proportion of patients with high adherence to the medications[45]. Additional predictors of non-adherence were dosing frequency and medication regimen complexity.

Additional studies have found a link between high medication-possession ratio and lower risk of graft failure[46]. Persistent non-compliance has been associated with increased immunosuppression and non-immunosuppression costs with persistently non-compliant patients experiencing 3-year medical costs of approximately $33000 more than patients with excellent compliance[36].

A 2014 study of renal transplant patients in the United Kingdom examined the budgetary impact of switching from tacrolimus-BID to extended release tacrolimus using a budget-impact model[44]. The model assumed that patients were taking a tacrolimus dose of 0.075 mg/kg per day 1 year post-transplant and that patients were taking concurrent MMF and corticosteroids based on a 2010 study[3]. Adherence rates were modeled after two studies, the first of which found that 88.2% of patients on extended release tacrolimus were adherent compared to 78.8% on tacrolimus-BID (P = 0.0009). The second study found that 11.8% of extended release tacrolimus patients were non-adherent, compared to 21.2% of tacrolimus-BID patients and that the risk of graft failure is 7.1-fold higher in non-adherent patients than in adherent patients[46]. The model assumed that all

patients with graft failure were started on dialysis (15% peritoneal dialysis and 85% hemodialysis). Pharmacy costs were derived from the British National Formulary and dialysis costs were taken from the National Health Service tariff information.

The base-case analysis, which assumed maximum relative risk of graft failure with non-adherence found that the average cost for patients taking extended release tacrolimus was £29328 (approximately $45750 based on a current exchange rate of 1.56) over 5 years compared to £33061 ($51575) for patients taking tacrolimus-BID for a savings of £3733 ($5825) per patient over 5 years. The cost savings related to extended release tacrolimus were primarily driven by lower projected rates of graft failure in this group (21.6% for tacrolimus-BID *vs* 18.3% for extended release tacrolimus). Decreased rates of graft failure were driven by higher adherence rates in this group (88.2% for extended release tacrolimus *vs* 78.8% for tacrolimus-BID). Of note, the cost of tacrolimus in the United Kingdom study was £12910 ($20139) for extended release tacrolimus to £14467 ($22568) for tacrolimus-BID over 5 year which amounts to a savings of £1557 ($2430) on direct medication cost. In the United States, the per milligram price of extended release tacrolimus is approximately twice that of tacrolimus-BID and may vary depending on wholesaler price and institutional contract, which may vary significantly from institution to institution in the United States. Pharmacy cost data was derived from the British National Formulary in the United Kingdom study[11]. Obvious differences between the United States healthcare system and the single-payer system in the United Kingdom may also limit the applicability of this analysis in the United States.

Based on the findings of the United Kingdom study, use of extended release tacrolimus may result in significant savings over 5 years when compared to immediate tacrolimus-BID. It is important to consider that these findings are predicated upon the assumption that once-daily dosing improves adherence and that improved adherence reduces the incidence of graft failure[47].

CONCLUSION

Overall extended release tacrolimus has a very similar safety and efficacy profile to tacrolimus-BID. It is currently approved to prevent rejection in kidney transplant recipients. It is however, not recommended in the used of liver transplant patient's due to the increased risk of mortality in female recipients. There has been minimal data regarding the use of extended release tacrolimus in heart and lung transplant recipients. Currently there is no data for the use of extended release tacrolimus in multiple organ transplants, pancreas or small bowel, this is an area where further studies need to be conducted. With the current data available for all organ groups the extended release tacrolimus should be dosed in a 1:1 fashion, the exception may be the CF population where their initial dose may need to be higher. Another important note in regards to extended release tacrolimus is that data has shown that extended release tacrolimus exposure was lower than tacrolimus-BID within the first week of transplant, however after that exposure was similar.

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