

Prevention of organ rejection in renal and liver transplantation with extended release tacrolimus

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Abstract: Tacrolimus is the key immunosuppressant used to prevent allograft rejection in kidney and liver transplant recipients. Despite the efficacy of tacrolimus and adjunctive immunosuppressants, a substantial number of patients experience episodes of acute rejection and late graft loss. Nonadherence is an etiological factor in both acute rejection and graft loss. In 2007, a prolonged release version of tacrolimus became available that allows once daily administration, thus halving the pill burden compared to the standard twice-daily tacrolimus. An increasing number of studies in de novo transplantation and in treatment conversion have evaluated the pharmacokinetic profile, efficacy, and safety of prolonged-release tacrolimus. We have reviewed the literature on the use of prolonged-release tacrolimus and hope that this will be of value in the design of protocols for transplant immunosuppression.

Keywords: immunosuppression, kidney, hepatic, allograft, adherence

Introduction

Transplantation of allogeneic organs into immunocompetent hosts typically leads to immune-mediated destruction of the organ. The development of immunosuppressive drugs that effectively prevent organ rejection has led to transplantation being the preferred treatment for end-stage renal failure and the only treatment for liver failure. In contemporary clinical practice, cell-mediated immunity driven by activated T cells is the predominant mode of rejection, though antibody-mediated rejection may also occur, most typically in the acute phase. Calcineurin inhibitors (CNI) have become the cornerstone of immunosuppressive regimens for both kidney and liver transplantation.

The two CNIs in common use are cyclosporine and tacrolimus. Tacrolimus forms a complex with FK506 binding protein (FKBP12), which inhibits the enzymatic phosphatase activity of calcineurin. This abrogates the calcineurin-dependent activation of nuclear factor of activated T cells transcription factor, causing a reduction in interleukin 2 production and, consequently, in T cell activation and proliferation. The robust efficacy of CNI-based regimens has been associated with a reduction in the cumulative incidence of a first episode of acute rejection to less than 20% at 60 months post-transplantation, and a 5-year graft survival of 73% and 84% for deceased donor and living kidney donor recipients, respectively, in the US.¹ A number of studies have shown that tacrolimus can be somewhat more effective than cyclosporine in preventing acute rejection and allograft failure.²⁻⁵

Since tacrolimus was licensed for liver and kidney transplantation in the 1990s, it has become progressively more popular, such that, by 2010, it was a component of about 90% of immunosuppression regimens for kidney or liver transplant recipients

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in the US.^{1,6} Nevertheless, as with cyclosporine, tacrolimus has a narrow therapeutic index and requires trough drug-level monitoring to confirm therapeutic levels and avoid toxic levels. Excessive immunosuppression increases the risk of infectious, metabolic, and malignant complications, whilst subtherapeutic levels allow acute rejection and organ failure. In the case of calcineurin inhibitors, high levels are also associated with significant nephrotoxicity.

Tacrolimus was initially developed as an immediate release preparation that is taken twice daily to maintain consistent therapeutic levels (herein referred to as TAC BID). In 2007, Astellas Pharma Inc. (Tokyo, Japan) marketed a prolonged release version (herein referred to as TAC QD) in Europe with the aim of reducing pill burden and improving adherence. The tacrolimus component itself remains unchanged but is encased in a capsule that delays tacrolimus release and absorption. Suboptimal adherence is thought to be a major contributing factor to allograft failure, particularly in kidney transplant recipients for whom a viable alternative exists in the form of dialysis.⁷⁻⁹ In general, adherence is better with once daily compared to twice daily medications.¹⁰ Furthermore, the evening dose is more often omitted than the morning dose. In addition to improving compliance, the altered pharmacokinetic profile of TAC QD could have a beneficial influence on side effects.

Since the development of TAC QD, many studies have evaluated its pharmacokinetic profile, efficacy, safety, and effect on adherence. In this article, we review the data comparing the use of TAC QD to TAC BID in both the stable conversion and de novo transplantation settings.

Methods

We performed a literature search of the PubMed and Web of Science databases in April 2014 using search terms comprising: “extended release tacrolimus or prolonged release tacrolimus” and “kidney or liver”. We manually reviewed the studies and considered only those that had more than five participants, were written in English, and for which the full text manuscript was available. In addition, further studies were manually curated from the reference lists of each manuscript.

De novo renal transplantation

TAC QD has been evaluated against TAC BID in six randomized controlled trials for the prevention of rejection in de novo kidney transplant recipients (Table 1).¹¹⁻¹⁶ In 2013, a systematic review that included five of these studies concluded that there were no differences in biopsy-proven acute rejection

or patient survival.¹⁷ The review included one randomized controlled trial in abstract form that used an alternative preparation of modified release tacrolimus, tacrolimus-LCP (LifeCycle Pharma, now Veloxis Pharmaceuticals, Hørsholm, Denmark), that has different pharmacokinetic parameters to the more commonly used TAC QD preparation, which is the Astellas Pharma Inc. product Advagraf/Astragraf XL.¹⁸ The largest randomized controlled trial, the open-label Optimising Immunosuppression After Kidney Transplantation with ADVAGRAF (OSAKA) trial, randomized 1,251 patients to four different treatment arms comprising TAC BID 0.2 mg/kg, TAC QD 0.2 mg/kg, TAC QD 0.3 mg/kg, and TAC QD 0.2 mg/kg plus basiliximab plus steroid avoidance.¹¹ All patients received mycophenolate and steroids except for the basiliximab group. Trough tacrolimus levels were initially higher in the arm taking 0.3 mg/kg TAC QD, but were similar from day 14 onwards and, at week 24, the median tacrolimus concentrations were between 7.7 and 8.3 ng/mL across all four arms.¹¹ In all arms, the dose tended to decrease over the duration of the study and was slightly higher overall in the TAC QD groups. The investigators assessed TAC QD efficacy for noninferiority based on a composite primary endpoint of graft loss, biopsy-confirmed acute rejection, or an modified diet in renal disease (MDRD) estimated glomerular filtration rate (eGFR) <40 mL/min/1.73 m². Noninferiority was only demonstrated for TAC QD 0.2 mg/kg compared to TAC BID 0.2 mg/kg (primary endpoint reached in 42.2% versus 40.6%, respectively), but was not demonstrated in the steroid avoidance TAC QD group (treated with additional basiliximab) or in the higher dose TAC QD group.¹¹ The seemingly high failure rate of the primary outcome was influenced by the high number of extended criteria donor organs (50%) contributing to an eGFR below the threshold of 40 mL/min/1.73m².¹¹ Similar numbers of patients experienced biopsy-proven acute rejections across the four arms (10.3%–16.1%). TAC QD was also found to be noninferior when compared to a cyclosporine-based immunosuppression regimen with follow-up to 12 months.¹⁶ The other four randomized trials also found no significant difference in graft survival or biopsy-proven acute rejection to a maximum of 12 months follow-up.¹²⁻¹⁵ Overall, the results of these randomized trials suggest that the efficacy of TAC QD is similar to that of TAC BID using a similar initial starting dose.

Investigators have sought more subtle indications of benefit arising from the altered pharmacokinetic profile of a once-daily drug. The rate of toxic tubulopathy in protocol biopsies did not differ between TAC QD and TAC BID.¹² However, concomitant pharmacokinetic analysis

Table 1 Studies in de novo kidney transplantation

Reference	Author	Year	Design (FU=follow-up)	Number of participants	Treatment	Outcome (AR=acute rejection, BPAR=biopsy proven acute rejection)
11	Albano	2013	Open label, parallel group randomized European adults being transplanted or re-transplanted, FU 24 weeks.	1251 (976 per protocol)	1-3 MMF + steroids 4 mycophenolate + basiliximab + periop steroids 1 TAC BID 0.2 2 TAC QD 0.2 3 TAC QD 0.3 mg/kg 4	TAC QD 0.2mg/kg was noninferior to TAC BID 0.2mg/mL (with steroids, MMF).
12	Tsuchiya	2013	Open label and prospective randomized controlled trial, FU 1 year.	102 (50 TAC QD)	Low dose TAC BID or QD. (6-10ng/mL induction, 4-6ng/mL maintenance	Protocol biopsy—overall 13.7% AR; no significant difference between groups. No significant difference in TAC tubulopathy or eGFR between groups. QD TAC dose was higher at most time points. The trough concentrations, peak levels and AUC were similar (AUC 280ng hour/mL at 14 days). There were no difference adverse events.
13	Krämer	2010	Multi-center 1:1-randomized parallel-group, noninferiority, double blind Phase III study, FU 24 weeks + open extension 12 months.	667	Pre-op 0.1 mg/kg, post op 0.2mg/kg	PE – noninferiority; rates of BPAR at 24 weeks were 15.8% vs 20.4% for TAC BID vs QD (P=0.182). The 12 month patient survival was 97.5% vs 96.9%, and graft survival 92.8% vs 91.5%. Renal function and adverse events were similar in each group. There was no difference in trough levels from 24hrs to 6 months. There was good correlation between AUC and trough levels at 3 days. Renal function remained similar between groups. The BPAR was 0% and 16%, for TAC QD and BID, respectively.
14	Cabello	2010	Randomized 1:1 comparative study, de novo renal transplant (expanded criteria donor, elderly recipients) FU 6 months.	27	TAC QID vs BID, 0.1 mg/kg	PE – The PK profile on day 1 showed an AUC for TAC QD as 30% lower but similar to TAC BID by day 14. The trough levels were similar by day 4. There was good correlation between AUC and trough levels. The efficacy and safety were similar between TAC QD and BID. In a 1yr extension (QD patients) – graft survival was 100% and 93.3% of patients were free from BPAR.
15	Wlodarczyk	2009	Open label randomized comparative study, centers in Europe and Australia. FU 6 weeks.	122 randomized (66 PK profiles) 47 extension phase 1yr	TAC BID or QD	PE – TAC BID/QD+MMF regimens were noninferior to Cyclosporine+MMF at 1 year based on a composite efficacy failure endpoint. The 1 year patient and graft survival for TAC QD was 98.6%, and 96.7% respectively. Similar safety of TAC QD with BID. Doses required were higher in TAC QD treated patients (P<0.01) but trough levels and renal function remained similar. Protocol biopsy – subclinical rejection rates were similar between TAC QD and BID. The presence of IF and TA was less with TAC QD vs BID (42.2 vs 20.6%, P=0.04). Allograft rejection (borderline or above) was associated with IF/TA. No difference in tubular vacuolization or arteriolar hyaline change was seen between groups.
16	Silva	2007	Randomized, Phase III, open label, FU 12 months.	638	TAC BID, QD or cyclosporin.	The trough level and AUC were similar between groups, with a higher median dose used in TAC QD patients.
19	Masutani	2014	Retrospective observational study de novo LRD renal transplant FU 12 months.	119 (29 TAC QD)	TAC QD vs BID	
20	Jelassi	2011	Observational study with control group, FU 18 days.	12 (+ 18 controls)	TAC QD vs BID	

(Continued)

Table 1 (Continued)

Reference	Author	Year	Design (FU=follow-up)	Number of participants	Treatment	Outcome (AR=acute rejection, BPAR=biopsy proven acute rejection)
21	Andrés	2010	Retrospective single center observational study, with control group, FU 3.5-4 months.	49 (+30 controls)	TAC QD vs BID	Acute rejection rates were 10%, and 13% for TAC QD and BID, respectively. TAC QD patient survival was 98%, graft survival 96%, vs 100% survival and graft survival of 90% in TAC BID patients. The day 14 TAC QD level was 36% lower, and dose 21% higher in TAC QD patients. Day 1 – there was a 16% decrease AUC with TAC QD. By day 3 exposure was similar. Trough levels were well correlated with AUC.
22	Włodarczyk	2012	Sub-study of randomized Phase III trial.	34	TAC QD vs TAC BID	In the TAC QD group, 3 month trough levels were lower, and at 12 months nonsignificantly lower. A significantly higher dose was required with TAC QD at 3 months and nearly identical at 12 months. Protocol and ad hoc biopsies showed AR in 4.3% and 11.1% for TAC QD and BID, respectively. Renal function was similar between groups.
23	Kirada	2012	Retrospective observational study, FU 1 year.	50	TAC QD (oral) or BID (IV then oral)	Applied a model with TAC to measure TAC exposure with levels measured at 0, 1, 3 hours post-dose – this estimated AUC accurately (bias=0.1%) with good precision. Efficacy and trough levels were similar with TAC QD or BID with increased dose in QD recipients. The trough level and AUC was 25% lower with TAC QD at day 28. Dose adjusted AUC in CYP3A5*1 carriers was 25% lower than CYP3A5*3 for TAC QD. Reduced inter-patient variability was seen with TAC QD. ABCBI 3435C>T polymorphism had no effect.
24	Woillard	2011	Retrospective observational study, FU 12 months.	41 TAC QD 32 TAC BID	TAC QD vs BID	TAC QD – patient and graft survival were 100% at 15.7 months with no cases of BPAR using higher doses with TAC QD.
25	Crespo	2009	Retrospective observational study with historical controls, FU 6 months.	26	TAC QD vs BID	Genotype of CYP3A5 was significantly correlated with bioavailability (lowest with *1/*1). There was no effect of ABCBI alleles. The CYP3A5*1 and CYP3A5*3 significantly lower bioavailability in QD group compared to the BID group. Adverse event rates were as expected for TAC based therapy.
26	Niioka	2012	Observational retrospective study, FU 28 days.	72	TAC QD vs BID	There was similar renal function, NODAT, BK viremia, AR, and graft survival with TAC QD and BID. With TAC QD fewer dose adjustments were needed to reach steady state (P=0.03).
27	Ishida	2013	Retrospective observational study.	10 (+ 35 controls)	TAC QD vs BID	
28	Niioka	2013	Retrospective observational.	97	TAC QD or BID	
29	Takahashi	2014	Open label prospective non-comparative, nonintervention, observational study, FU 24 weeks.	256	TAC QD	
30	Fanous	2013	Retrospective, observational study, FU 12 months.	106 TAC QD 95 historical control TAC BID	TAC QD vs BID	

31	Hooff	2011	Open-label single-arm, follow up study of four Phase II studies – 2 de novo (kidney, liver), 2 stable conversion (kidney, heart) > 90% Caucasian, FU 4 years.	240 (entry 6 weeks after de novo, 12 weeks after conversion)	TAC QD vs BID	Patient and graft survival were over 90% and freedom from BPAR was 90.0% with TAC QD.
32	Schenker	2009	Prospective observational study, FU 11 months, simultaneous pancreas-kidney transplantation.	14	TAC QD	Overall survival rates: patient—100%, kidney graft—100%, pancreas graft—93%. AR occurred in 38% of patients and 1 patient discontinued TAC QD due to psychotic symptoms.

Abbreviations: AR, acute rejection; AUC, area under the curve; BID, twice daily; BPAR, biopsy-proven acute rejection; FU, follow-up; QD, once daily; IF, interstitial fibrosis; TA, tubular atrophy; LRD, live related donor; MMF, mycophenolate mofetil; NODAT, new onset diabetes after transplantation; PE, primary endpoint; PK, pharmacokinetic; TAC, tacrolimus; eGFR, estimated glomerular filtration rate.

did not reveal any difference in the area under the curve of the drug concentration over time (AUC) or in peak drug levels on day 14.¹² A retrospective study analyzing protocol biopsies in living related donor kidneys for features of CNI toxicity and subclinical rejection up to 12 months post-transplant found no significant differences, but there was a trend to reduced interstitial fibrosis/tubular atrophy.¹⁹

Adverse events were equally common across TAC BID and QD treatment arms in randomized controlled trials.^{11–16} Specifically, there was no significant difference in indices of glucose metabolism.

The majority of studies where AUC has been assessed have reported that trough levels were highly correlated, and these studies recommend routine clinical monitoring using trough levels.¹⁵ The manufacturer's recommendation of close monitoring in the first 2 weeks to ensure therapeutic levels is based on a study that showed an initial 30% lower AUC after the first day.¹⁵ By day 14, levels were comparable in TAC QD and TAC BID groups.¹⁵ One study found that, for patients taking relatively high doses of tacrolimus, the AUC was in a therapeutic range despite subtherapeutic trough levels, indicating that occasional AUC assessment may be useful in routine clinical practice with TAC QD.²⁰ Older patients (>60 years old) have been found to require lower doses of TAC QD than younger patients to achieve therapeutic trough levels.²¹

The efficacy and safety data from 14 additional observational studies are consistent with the randomized controlled trial data (Table 1).^{19–32} Although the effect of TAC QD versus TAC BID on adherence in de novo transplantation has not been systematically tested, an industry-sponsored modeling analysis that extrapolated the effect on adherence, as well as outcomes from a literature review of other studies of twice-versus once-daily medication, suggested that, after 5 years, graft survival would be 6.1% higher in the TAC QD group, which would result in a cost saving of US \$9,411 per patient over the 5 years.³³

TAC QD is a useful treatment option that may reduce pill burden in patients adapting to life after transplantation, but an advantage in terms of efficacy or safety has not been demonstrated.

De novo liver transplantation

The efficacy and safety of TAC QD in patients undergoing liver transplantation was confirmed by a substantial double-blind randomized controlled trial with 475 participants (Table 2).³⁴ Patients were initially treated with tacrolimus (TAC BID or TAC QD) and steroids, with antiproliferative

Table 2 Studies in de novo liver transplantation

Reference	Author	Year	Design	Number of participants	Treatment	Outcome
31	Hooff	2011	Open-label single-arm, follow up study of four Phase II studies – 2 de novo (kidney, liver), 2 stable conversion (kidney, heart) >90% Caucasian.	240 (entry 6 weeks after de novo, 12 weeks after conversion)	TAC QD vs BID	Patient and graft survival was over 90%. Freedom from BPAR was 92.6% for de novo liver transplantation.
34	Trunečka	2010	Multi-center I: I-randomized, two-arm, parallel-group, double blind 24 weeks study + open extension 12 months.	475	TAC QD or BID	TAC QD was non-inferior; BPAR by 24wks occurred in 33.7% and 36.3% of patients for TAC BID and TAC QD (P=0.512), respectively. The BPAR requiring treatment rate at 12 months was 28.1% and 24.7% for TAC BID vs QD respectively. Adverse events profiles were similar. In the first 24 hours the AUC was 50% less with TAC QD. At 14 days the AUC was comparable but with higher QD doses. There was a strong correlation between AUC and trough levels. The efficacy at 6 weeks was similar.
35	Fischer	2011	Randomized Phase II, multicenter, open label trial, FU 6 weeks.	129 (PK data for 77 patients)	TAC QD vs BID 0.10-0.15 mg/kg	TAC IV was converted to oral by a mean of 15.4 days. LFTs, glucose and renal function remained stable. The average conversion period duration was 4.6 days. There were no significant differences in AUC pre/post conversion using dose adjustment based on trough levels. The optimal initial dose conversion ratio from IV to oral was 1 to 8.
36	Mita	2014	Prospective open label observational study, FU 1 week.	10	TAC IV to TAC QD conversion	Overall adverse event rates: BPAR 10%, NODAT 22%, HTN 18%, 6% creatinine => 1.5mg/dL with 100% patient and graft survival.
37	Urbina	2011	Retrospective analysis, FU 6 months.	50	TAC QD 1.5mg/kg or 0.75mg/kg	BPAR occurred in 13% of patients and graft survival was 100%. There was no change in mean glucose level and no cases hepatitis C relapse.
38	Charco	2011	Prospective, observational, multicenter, longitudinal, 3-month study.	52	TAC QD	Infection related adverse events occurred in 25%, including CMV viremia in 12.5% of patients. Patient and graft survival at 1 year was 94.1% and 94.1%, respectively with AR occurring in 20.8% of patients. More frequent dose adjustments were required with TAC QD. Higher total exposure occurred in TAC QD treated patients. There was no change in renal dysfunction, AR, length of stay.
39	Uemoto	2014	Prospective, open label nonintervention, observational study, FU – de novo 1yr, conversion – 24 weeks	De novo 24 Conversion 122	TAC QD de novo or conversion from TAC BID	There was similar AUC and safety profile with conversion (renal and liver function stable with no AR).
40	Marubashi	2012	Nonrandomized cohort study with historical controls, FU 90 days.	16 (+14 historical controls)	TAC QD vs BID	Abbreviations: AR, acute rejection; AUC, area under the curve; BID, twice daily; BPAR, biopsy-proven acute rejection; FU, follow-up; IV, intravenous; PK, pharmacokinetic; QD, once daily; TAC, tacrolimus; NODAT, new onset diabetes after transplantation; LFT, liver function tests; CMV, cytomegalovirus; HTN, hypertension.
41	Sugawara	2011	Open label single center study, FU 20 weeks	12 (9 completed study)	iv TAC to TAC QD	

Abbreviations: AR, acute rejection; AUC, area under the curve; BID, twice daily; BPAR, biopsy-proven acute rejection; FU, follow-up; IV, intravenous; PK, pharmacokinetic; QD, once daily; TAC, tacrolimus; NODAT, new onset diabetes after transplantation; LFT, liver function tests; CMV, cytomegalovirus; HTN, hypertension.

agents allowed only after an acute rejection episode. In this noninferiority study, the primary endpoint of biopsy-proven acute rejection at 24 weeks occurred in 33.7% of patients receiving TAC BID and 36.3% of patients receiving TAC QD ($P=0.512$). Additional follow-up after an open-label extension to 12 months showed similar rates of biopsy-proven acute rejection requiring treatment (28.1% and 24.1% for TAC BID and TAC QD formulations, respectively). In the early postoperative phase, TAC levels were higher in the TAC QD group at day 7 (12 ng/mL versus 9.5 ng/mL, $P<0.005$), but patients were initiated on twice the daily total dose of TAC QD due to concerns raised by other studies of reduced exposure in the early phase of TAC QD treatment. No clear correlation between early exposure and biopsy-proven acute rejection was demonstrated. The authors reported that the majority of patients received tacrolimus via nasogastric tube in the postoperative period despite TAC QD consisting of extended release capsules. Nevertheless nasogastric administration did not significantly affect pharmacokinetic profiles. Adverse events were similar between the two groups, although TAC QD was associated with higher mortality than TAC BID in female patients (18.4% versus 7.8%); the cause for this finding remains unclear.

A further randomized open-label trial compared the pharmacokinetic profile and efficacy of TAC QD versus TAC BID in the first 6 weeks after liver transplantation.³⁵ Both forms of tacrolimus were administered at a similar starting dose (0.1–0.15 mg/kg) and this resulted in an AUC that was 50% lower in TAC QD patients. However, with dose adjustments, a similar AUC was reached by day 14 (TAC QD 324 vs TAC BID 287 ng.h/mL), using a higher mean dose in the TAC QD group.³⁵ As with TAC QD usage in de novo kidney transplants, the manufacturer recommends careful monitoring in the first two weeks. At 6 weeks, the AUC was again similar for TAC QD and TAC BID, although TAC QD patients were maintained on a higher dose (TAC QD 0.209 mg/kg; TAC BID 0.165 mg/kg).³⁵ The secondary endpoints of efficacy and safety were similar in both groups at 6 weeks, with biopsy-proven acute rejection occurring in 26.9% and 27.4%, respectively.³⁵ Patients were not allowed to receive TAC QD by nasogastric tube, but patients in the TAC BID group were allowed to receive the contents of the capsule. In terms of therapeutic drug monitoring for TAC QD, trough levels and AUC were well correlated, allowing routine clinical dose adjustments to be made based on trough levels as for TAC BID.³⁵

A smaller study examined the pharmacokinetics of converting intravenous tacrolimus to oral TAC QD, which may

be useful for patients who are unable to take oral medication in the immediate postoperative period.³⁶ Ten patients received intravenous tacrolimus that was converted to oral TAC QD by a mean of 14.5 days. Conversion was performed gradually over several days and trough-tacrolimus levels were consistently maintained. The authors suggested that the most suitable final dose conversion ratio was 1:8.³⁶ The manufacturer has recommended intravenous administration at a fifth of the oral dose.

Other observational studies have yielded similar results regarding efficacy and safety (see Table 2).^{37–41} The effect on long-term adherence of using TAC QD in the immediate postoperative period has not been systematically studied. Several studies examined the effects of TAC QD on metabolic parameters, including glucose metabolism and these were not demonstrably improved compared to patients receiving TAC BID.^{31,34,37,38}

In liver transplantation, TAC QD appears similar in efficacy and profile to TAC BID, but a clear advantage has not been demonstrated and clinicians must be careful to avoid low levels in the first few days.

Conversion to TAC QD in stable adult kidney transplant recipients

The effect of switching to TAC QD in stable kidney-transplant patients has been extensively evaluated in observational crossover studies, but not in randomized controlled trials (Table 3). The largest crossover study, involving 1,832 patients, prospectively analyzed the effect of a 1:1 mg for mg conversion (1:1.1 for patients with known low trough levels) on efficacy, safety, and patient satisfaction.⁴² In these patients, the mean trough level was moderately reduced at 12 months (−9.1%) and the mean dose was marginally higher (+1.24%).⁴² The persistent reduced level at 12 months raises potential concerns that, over the longer-term, the altered pharmacokinetic profile could increase the risk of subclinical rejection. During the study, TAC QD appeared to be efficacious, with only eight patients developing acute rejection and no overall change in eGFR or proteinuria.⁴² Other cardiovascular and metabolic parameters also remained unchanged, including blood pressure, lipids, glucose, and liver function tests.⁴² Overall 99.4% of patients preferred once-daily tacrolimus and the discontinuation rate was only 1.9%.⁴² Other smaller studies have generally been consistent with these results and, most notably, variously show modest reductions in tacrolimus trough levels with no apparent effect on acute rejection (see Table 3), with follow-up ranging from several weeks to 4 years.^{18,31,43–75}

Table 3 Studies of conversion to TAC QD in stable adult kidney transplant recipients

Reference	Author	Year	Design	Number of participants	Treatment	Outcome
18	Gaber	2013	Prospective conversion study using TAC-LCP, FU 21 days.	47	TAC BID to QD (LCP-Tacro tablets -Veloxis)	The mean conversion ratio was 1:0.71 resulting in consistent AUC and trough level after lower conversion dose. There were reduced fluctuations in levels after conversion ($P<0.0001$). 30% lower dose was required with TAC QD to maintain similar levels. Note—different preparation to Advagraf with increased bioavailability. Patient and graft survival was over 90%. Freedom from BPAR was 100% after conversion. Renal function remained stable.
31	Hooff	2011	Open-label single-arm, follow up study of four Phase II studies – 2 de novo (kidney, liver), 2 stable conversion (kidney, heart) >90% Caucasian	240 (entry 12 weeks after conversion)	TAC BID to QD	Trough level decreased (mean at 12 months –9.1%) and the dose was increased by 1.24%. There was no change in eGFR, proteinuria, BP, lipids, LFTs, and glucose parameters. 8 patients developed AR (0.4%) and 34 discontinued TAC QD. 99.4% of patients preferred the once daily formulation.
42	Guirado	2011	Multicenter prospective observational study, FU 12 months.	1832	TAC BID to QD 1:1	TAC dose remained similar with a nonsignificant decrease in trough levels (–12%). Renal function remained stable and there were 14 cases AR. Graft survival at 1 year was 96.3%. 28 patients discontinued TAC QD.
43	Slatinska	2013	Retrospective observational crossover study, up to 12 month FU	589	TAC BID to QD 1:1	Conversion resulted in lower variation in blood levels and decreased trough levels. Renal function remained stable and there was a significant decrease in mean blood glucose levels. Fewer dose changes were required after conversion.
44	Kurnatowska	2011	Retrospective single center analysis, FU – 6 visits before/after (mean observation time after conversion 420 days)	52	TAC BID to QD	At baseline nonadherence was 23.5% and associated with previous rejection episode ($P<0.002$), lower life satisfaction index, anxiety, low GFR ($P<0.03$) and reduced satisfaction with medical care/medical staff. After conversion there was increased adherence (+36%, $P<0.05$ vs basal). Trough levels decreased (–9%) despite an increased dose (+6.5%).
45	Sabbatini	2014	Cross-sectional and prospective open label nonrandomized conversion observational study, FU 6 months	310 (121 converted to TAC QD)	TAC BID to QD	Trough TAC level decreased from 4.2 to 3.5 ng/mL (99 patients had a drop >20%). There was no change in renal function, lipids or glucose. 17% of patients discontinued TAC QD. Mean time from transplant to conversion was 8.3 years. When discontinuation occurred it was often initiated by patient concerns.
46	Wu	2013	Retrospective cohort study of crossover, Chinese participants, FU 6 months.	199	TAC BID to QD 1:1.1.1.2	Trough levels decreased and dose was escalated after conversion with no episodes of acute rejection.
47	Ma	2013	Prospective open label study with Chinese participants, FU 12 weeks. + FU at 52 weeks (off protocol).	20 (two violated protocol)	TAC BID to QD 1:1	

48	Sessa	2012	Observational longitudinal study of crossover to TAC QD	40	TAC BID to QD 1:1 conversion	Blood uric acid and homocysteine levels improved significantly after conversion. Numerical improvement in renal function (non-significant). Steady state level comparable for QD and BID. No change in renal function over the 8 week period. AUC and trough levels were well correlated.
49	Hooff	2012	Open-label, multicenter replicate design study	69 (60 completed protocol)	TAC QD vs BID – 1:1 dose, 4 sequential 14 day cycles of alternating QD or BID.	Mean trough TAC level decreased after conversion (4.55 to 3.2ng/mL). There was no significant change in renal function, lipid or glucose levels and no AR or infection. The change in creatinine clearance showed noninferiority, no BPAR, and no discontinuations. 59.1% required a dose change, and were mostly increases.
50	Nakamura	2012	Observational conversion study, Japanese participants, FU 2 months	33	TAC BID to QD 1:1	After conversion TAC trough levels decreased (4.9ng/mL to 4.24ng/mL) and renal function remained stable. Homeostasis model assessment of Beta-cell function, glycosylated hemoglobin levels and fasting insulin decreased significantly after conversion.
51	Lauzurica	2012	Multicenter, open, Phase IIIb study, FU 12 weeks, mainly Caucasian	128 enrolled 91 evaluated for PE	TAC BID to QD 1:1	TAC trough levels decreased (6.6 to 5.4ng/mL) and peak levels decreased with no change in AUC. There was no change in insulin sensitivity or insulin secretion.
52	Uchida	2012	Prospective, observational, crossover, FU 4 weeks	26	TAC BID to QD 1:1	eGFR increased at 12 (eGFR 57.1 to 60) and 24 months (eGFR 66).
53	Midtvedt	2011	Prospective crossover study. FU 4-6 weeks Caucasian	20	TAC BID to QD 1:1	There was decreased dose-adjusted AUC in both groups. Trough levels were similar for non-expressors, and decreased in the expressor group (8.2 to 6.3ng/mL).
54	Kolonko	2011	Retrospective, crossover, stable renal TX (+SPK) FU 24 months	72	TAC BID to QD	Renal function remained stable. The TAC level decreased initially then normalized (6.9ng/mL baseline, 4.7ng/mL 3 months, 5.2ng/mL 6 months, 6.2ng/mL 12 months). There was no dose difference.
55	Glowacki	2011	Prospective, single center, open-label study	17 (CYP3A5*1/#3 or 1/1) 15 (CYP3A5*3/#3)	TAC BID to QD 1:1	The trough level decreased by 12.66% with a >20% decrease in 38.3% patients. The dose was increased in 52.5% patients and 28% patients required a dose increase of >20%. Dose changes were greater in the 1st year. Increased creatinine and lower hemoglobin was associated with increased dose requirement. Overall trough levels remained 9.09% lower.
56	Iaria	2011	Observational conversion, FU 19 months	41	TAC BID to QD 1:1	Renal function remained stable, 7% of patients required dose decreases, 21% patients dose increases, and 16% of patients required a >30% dose increase. In South Asians 8% patients required a dose increase of >30%, East Asians 27.5% patients required increase doses >30% with similar baseline dose.
57	Jonge	2010	Retrospective single center study, conversion, FU 6 months or until Oct 1 2009	284	TAC BID to QD 1:1	7.6% of patients required dose adjustment. There was an initial reduction in TAC trough level at 7 days was then stable. Renal function and proteinuria levels remained stable.
58	Glick	2014	Prospective observational study 40% ethnic minority, FU 3-18 months	496	TAC BID to QD	
59	Ojea	2009	Observational study, FU 90 days	82 (38 90 day FU)	TAC BID to QD 1:1	

(Continued)

Table 3 (Continued)

Reference	Author	Year	Design	Number of participants	Treatment	Outcome
60	Mecule	2010	Controlled crossover study, FU 6 months	40	TAC QD to BID 1:1	BP, renal function and cholesterol remained similar. Glycemia and triglyceride levels were reduced with TAC QD. 25% required TAC QD dose adjustment. There was no BPAR and TAC levels remained stable overall.
61	Tinti	2010	Observational crossover single center study, FU 6 months	31	TAC BID to QD	There was a small but significant decrease in TAC trough level after conversion. Renal function showed significant improvement after conversion (1.5 vs 1.6 mg/dl). There was no significant association between TAC trough level and renal function
62	Hougardy	2011	Retrospective observational crossover conversion study, FU 6 months	55	TAC BID to QD	The dose was significantly increased by 6 months. There was a decreased trough level at 180 days (8.05ng/mL to 6.3ng/mL). 35% patients required >30% dose increase. Renal function remained stable and there was no AR.
63	Wehland	2011	Crossover study, FU 1 year	41	TAC BID to QD	There was decreased trough and dose-normalized trough levels after conversion. Patients with the CYP3A5*3/*3 alleles required lower TAC doses of either BID or QD. There was a decline in trough TAC level after conversion in patients with *3/*3 alleles.
64	Calla	2011	Prospective observational cross-over study, FU 6 months	78	TAC BID to QD	49 patients agreed to convert. There was no difference in baseline psychological variables. 8 patients switched back due to adverse events. Conversion resulted in increased patient initiated disclosure of having received a transplant ($P<0.05$). Patients who switched back showed less positivity and well-being ($P<0.05$)
65	Mecule	2011	Observational crossover study, FU 1yr	31	TAC BID to QD 1:1	TAC trough levels decreased ($P=0.024$) and in 19% of patients the dose was adjusted (50% patients increased dose). Similar rate of adjustment to pre-conversion and overall doses were similar.
66	Wu	2011	Prospective observational cross-over study, open label, single center, FU 3 months	129	TAC BID to QD	There was a nonsignificant increased dose (4.7mg to 4.9mg). Trough TAC level decreased significantly after conversion. In 41/129 patients the decrease was >25% at day 7. There was reduced intra-patient trough variability.
67	Uchida	2014	Prospective conversion study, FU 24 weeks	26	TAC BID to QD 1:1	The trough level decreased at 4 weeks and was comparable at 24 weeks after dose increases. HOMA-beta assessment was significantly higher after conversion.
68	Alloway	2007	2 year follow up of conversion study, FU 2 years	67	Previously converted TAC BID to QD	2 year patient and graft survival was 100% and 98.5%, respectively. The BPAR incidence was 6%, multiple rejection rate 1.5%, and overall safety profile similar to the known TAC BID profile.
69	Bäckman	2014	Prospective observational multicenter conversion study, FU 90 days	224	TAC BID to QD 1:1	Trough level was significantly decreased at day 14 and at 12 weeks. Dose was increased in 22% and reduced in 15.6% patients. Trough level increased in 36.5% and decreased in 62.5%. There was no AR or graft loss. After conversion 19% of patients forgot medication less frequently and 55% reported no difference. 55% felt the change in dosing schedule was "better".

70	Tsuchiya	2012	Crossover study, FU 120 days	43	TAC BID to QD 1:1	The trough level was comparable at 120 days. There was a significant increase in insulin and HOMA-Beta score ($P=0.091$). Renal function, glucose, and HbA1c levels remained stable.
71	Hatakeyama	2012	Prospective observational crossover study stable adult renal transplant Mean FU 14 months	12	TAC BID to QD 1:1	Trough level decreased from 4.8 to 3.6ng/mL within 1 month ($P=0.0002$). Renal function, potassium, glucose, HbA1c, and urine protein creatinine ratio remained similar.
72	Rostaing	2012	Prospective multicenter conversion study, FU 24 weeks	301	Cyclosporine to TAC QD	Renal function was noninferior after conversion with no AR. Patient and physicians reported cosmetic improvement.
73	Veroux	2012	Crossover study with historical control group, FU 1 year	57	TAC BID to QD	After conversion there was improvement in gastrointestinal (GI) symptoms ($P<0.001$), GI health quality of life ($P<0.05$). At 12 months there was significantly lower abdominal pain, diarrhea, and reflux.
74	Boekel	2013	Prospective cohort study crossover, FU 6 weeks	75	TAC BID to QD	Conversion resulted in increased satisfaction ($P<0.001$) and increased self-reported adherence (79.7% to 94.6%, $P<0.001$).
75	Wu	2014	Observational retrospective case control study	150	TAC BID vs TAC QD	CYP3A5 low expressor genotype had significantly higher trough TAC levels. In the high expressor group the coefficient of variation of trough levels was significantly reduced in the QD group.
76	Bunnapradist	2013	Phase III noninferiority trial of efficacy/safety conversion study, FU 12 months	326	TAC BID vs QD (tacrolimus-LCP)	There was no difference in the proportion with efficacy failure and safety was similar. There was increased discontinuation with TAC QD (12% vs 5%, $P=0.028$). The trough levels were similar. The dose in the QD group was lower than BID ($P<0.0001$) but starting dose higher. Note LCP formulation.
77	Alloway	2005	Open-label, multicenter study with crossover design, FU 21 days	70 (66 completed all PK profiles without error)	TAC BID to QD	Renal function remained stable with comparable safety profile and was well tolerated. AUC was highly correlated with trough levels. 30% of patients required dose adjustment. Nonsignificant reduction in AUC and trough levels. There was no difference in subsets based on gender, African-American or diabetes. With TAC QD there was less intra-subject variability.
78	Muduma	2014	Cost modeling based on effects of intra-patient variability in trough TAC levels		TAC BID to QD	Predicted 5 year saving £3415 in TAC QD group, driven mainly by lower dialysis costs.
79	Kuypers	2013	Randomized, multicenter, controlled trial, FU 9 months Randomized 2:1	219	TAC BID to QD	At 6 months 18.5% discontinued TAC QD. Electronic adherence monitoring showed that 88.2% and 78.8% of TAC QD and BID treated patients, respectively ($P=0.0009$) took the prescribed number of doses. In the BID group the percentage of missed doses was higher in the evening (11.7% morning, 14.2% evening ($P=0.0035$)).

Note: Tacrolimus-LCP (veloxis Pharmaceuticals, Hørsholm, Denmark), Advagraf (Astellas Pharma inc., Tokyo, Japan).

Abbreviations: AR, acute rejection; AUC, area under the curve; BID, twice daily; BP, blood pressure; BPAR, biopsy-proven acute rejection; eGFR, estimated glomerular filtration rate; FU, follow-up; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin (A1c); HOMA, homeostasis model assessment; PE, primary endpoint; PK, pharmacokinetic; TAC, tacrolimus; QD, once daily; LFT, liver function tests; Tx, transplant; SPK, simultaneous kidney and pancreas.

One study reported improved fasting blood glucose levels with TAC QD (103.4 mg/dL versus 95 mg/dL, $P < 0.03$), but this may be in keeping with reduced trough levels in the TAC QD group.⁴⁴ Another once-daily tacrolimus preparation under development that has a different pharmacokinetic profile, Tacrolimus-LCP, showed noninferiority to TAC BID in a randomized Phase III conversion study.⁷⁶

The pharmacokinetic profile within 21 days of switching to TAC QD was studied in detail in 66 patients.⁷⁷ As with other patient groups receiving TAC QD, trough levels were highly correlated with AUC – a finding that supports routine clinical monitoring. A nonsignificant reduction in AUC and trough level was observed, but only 30% of patients required a dose change.⁷⁷ The manufacturer recommends a 1:1 mg for mg conversion of the total daily dose and also checking of a level prior to and within 2 weeks of conversion. As has subsequently be observed in other studies, there was less intrasubject variability in tacrolimus levels – a factor that, in a model-based analysis, was predictive of reductions in graft failure and consequent dialysis costs.⁷⁸

The effect of tacrolimus conversion on adherence has been assessed in a randomized controlled trial that used electronic recordings of pill bottle opening as an indirect objective measure, coupled with subjective questionnaire interviews.⁷⁹ Two hundred and nineteen stable patients were randomized to TAC QD or continuation of TAC BID and followed for 3 months prior to conversion as well as 6 months after.⁷⁹ At 6 months, persistence with the prescribed regimen was higher for TAC QD (81.5% versus 71.9%, $P = 0.0824$).⁷⁹ The number of patients taking the prescribed number of daily doses was significantly higher for TAC QD (88.2% versus 78.8%, $P = 0.0009$).⁷⁹ In keeping with data from other studies, patients were less adherent with the evening dose of TAC BID (missed doses: 11.7% morning versus 14.2% evening, $P = 0.0035$).⁷⁹ Adherence was also improved after conversion in several observational crossover studies using questionnaires, and no study found decreased adherence.^{42,45} However, despite this success, another study found a high discontinuation rate after conversion in patients who were about 8 years out from transplantation.⁴⁶ Discontinuation was primarily due to patient concerns and anxiety, presumably due to their aversion to changing from a long established and effective treatment.⁴⁶

Overall, despite the lack of randomized controlled trials studying the efficacy and safety of conversion to TAC QD, the plethora of observational conversion studies support TAC QD as a broadly equivalent treatment in terms of relatively short-term outcomes. However, the modest but persistently reduced levels found in some studies require long-term

follow-up data to analyze the effects on subclinical rejection and increased chronic allograft nephropathy and, conversely, on drug-induced nephrotoxicity.

Conversion to TAC QD in stable adult liver transplant recipients

We identified 17 studies examining the effects of conversion from TAC BID to TAC QD in stable liver transplant recipients (Table 4).^{39,69,80–94} The majority of the studies were observational crossover studies examining pharmacokinetic profiles and efficacy in patients before and after conversion. We did not identify randomized or blinded controlled trials. In almost all studies, a 1:1 mg for mg conversion of tacrolimus was used. In the majority of the 17 studies, tacrolimus levels were reduced after 1:1 conversion, but tended to normalize back to preconversion levels after physician-initiated dose increases in a subset of patients.^{69,80–86} However, this finding was not universal across all studies and, even in studies showing an initial mean decrease in trough levels, a subset of patients had higher levels after conversion.^{69,87} A detailed open-label multicenter prospective study investigated the pharmacokinetic effect of crossover using a four-period crossover design in which patients received TAC BID and TAC QD in alternating 14 day blocks.⁸⁸ Importantly, as with studies in de novo liver transplants, the AUC and trough levels were highly correlated, which supports routine clinical drug level monitoring using trough levels. Overall, after treatment with TAC QD, there was a nonsignificant 11.1% reduction in tacrolimus levels. Eighty percent of patients did not require a dose change and there was less inpatient variability in tacrolimus levels during TAC QD treatment. At 2-years follow-up of 56 patients maintained on TAC QD, the biopsy-proven acute rejection incidence was 5.6%, and the rates of infectious and metabolic complications were similar to those expected with TAC BID.⁹¹ Across these observational studies, there was no evidence of increased rejection rates despite initial reductions in trough levels in some patients, but no study had a follow-up of more than 2 years. In one study, renal function was significantly improved after conversion, with the MDRD eGFR rising from 71 to 82 mL/min ($P = 0.001$), but there was no control arm.⁸⁶ A change back from TAC QD to TAC BID was infrequent; a 24 month retrospective study of 394 patients found that only 16 patients switched back to TAC BID for various reasons, the commonest being tremor ($n = 3$).⁸⁵ Taken together, these data suggest that conversion to TAC QD is safe and efficacious. Since the effects on trough levels after conversion vary across individuals, robust monitoring may be required for the first few weeks to months to individualize dose levels.⁸⁵

Table 4 Studies of conversion to TAC QD in stable adult liver transplant recipients

Reference	Author	Year	Design	Number of participants	Treatment	Outcome
39	Uemoto	2014	Prospective, open label nonintervention, observational study, FU – de novo 1yr, conversion – 24 weeks.	Conversion 122	TAC QD de novo or conversion from TAC BID	Adherence of >90% increased from 84.1% to 96.5% post conversion. TAC trough level was 3.6ng/mL pre and 3.5ng/mL 1 week post-conversion.
69	Bäckman	2014	Prospective observational multicenter conversion study, FU 90 days.	Liver 19	TAC BID to QD 1:1	Significantly decreased trough levels at day 4 to 14 and 12-week time points with no significant change in dose. Dose increased in 22% and reduced in 15.6% patients. Trough levels were increased in 36.5% and decreased in 62.5%. There were no episodes of AR or graft loss. 19% of patients forgot their medication less frequently and 55% reported no difference. 55% felt change in dosing schedule “better”.
80	Weiler	2013	Prospective observational crossover single-center trial stable, FU 18 months.	61	TAC BID to TAC QD	With TAC QD 11 patients had dose escalations, and 10 dose reductions. Trough levels were significantly lower with TAC QD. There were no significant differences in clinical or biochemical parameters except for increased glycosylated hemoglobin with TAC QD.
81	Merli	2010	Crossover study adult, FU 6 months.	28	TAC BID to QD 1:1	In 43% of patients the dose was increased and in 24% the dose was reduced. TAC levels were stable by 45 days and there were no adverse events or changes in liver function.
82	Beckebaum	2011	Observational crossover study, FU 1 year.	125	TAC BID to QD 1:1	After 1 week trough levels decreased from 6.1ng/mL to 5.5ng/mL ($P=0.0016$), and after 2 weeks to 5.5ng/mL ($P=0.019$). In 28.8% of patients TAC level was >25% lower, 24% TAC >25% higher. TAC doses were increased by week 2, month 1 and month 3. TAC dose decreased at month 6 and 9 in 1/3 patients. LFTs, renal function and HBA1c remained stable, with no AR over 12 months. Nonadherence decreased from 62.4% to 36% ($P<0.0001$). Baseline adherence was significantly higher in patients converted >2 years after and if <60 years old.
83	Zhang	2011	Chinese open label multicenter study, one way conversion, FU 84.	83	TAC BID to QD 1:1	Day 1 AUC remained stable and at day 84 was reduced by 17%, deemed outside the bioequivalent range. Doses increase by 14% and there was good correlation between AUC and trough levels.
84	Dopazo	2012	Observational multicenter study, FU 6 months.	187	TAC BID to QD 1:1	There was significantly decreased trough levels at 1 month from 5.4ng/mL to 4.4ng/mL ($P=0.013$) and normalized by 6 months. LFTS remained stable overall and AR occurred in 2/187 patients.
85	Dumortier	2013	Retrospective, single center conversion study, FU 24 months.	394	TAC BID to QD 1:1	Trough level decreased after conversion ($P<0.05$). 9% patients discontinued TAC QD. LFTs, renal function, diabetes, dyslipidemia remained unchanged. 7 patients developed BPAR in the TAC QD group.
86	Giannelli	2013	Observational crossover study, FU 12-24 months.	65	TAC BID to QD 1:1	Dose stabilized in 90% of patients by 3 months after conversion. LFTS, glucose, lipids, and BP remained stable after conversion. There was significant improvement of renal function (MDRD GFR 71 to 82, $P=0.001$).

(Continued)

Table 4 (Continued)

Reference	Author	Year	Design	Number of participants	Treatment	Outcome
87	Comuzzi	2010	Observational conversion study, FU 14 days.	36	TAC BID to QD 1:1	There was no significant change in trough level or dose between times 0, 7 days, 14 days. LFTs and renal function remained stable with no AR. AUC decreased by 11.21% after conversion (not significant). 80% did not require dose adjustment. Intra-subject variability was less with TAC QD. There was a strong correlation between AUC and trough levels. Tolerability was similar and only 1 patient developed BPAR after conversion. There were no new cases of diabetes.
88	Florman	2005	Open label, multicenter, single sequence 4 period crossover design, FU 56 days (91.9% Caucasian)	72 (62 all 4 PK profiles)	Crossover TAC BID and QD. 1:1	Pill bottle opening was monitored electronically. Dosing compliance increased after conversion ($P=0.008$). Timing compliance significantly increased after conversion ($P=0.003$). The missed dose rate was twice as high in the TAC BID group. There was no difference in compliance changes between subgroups of patients converted at different times post-transplantation.
89	Eberlin	2013	Crossover study, FU 12 months	65	TAC BID to QD	Adherence visual analogue rating increased from 86 to 90% and BAAASIS score reduced from 45% to 35%. Renal function improved – 6mL/min increased clearance.
90	Valente	2013	Observational, retrospective crossover study, Stable adult, peripheral center, median FU 21 months.	34	TAC BID to QD 1:1	Mean dose remained fairly constant (range 5.5-6mg). Most patients did not require dose changes. BPAR incidence at 2 years was 5.8%. The incidence of infections and metabolic complications as expected for TAC. Renal function remained stable. 74.5% required no dose adjustment and trough levels decreased from 7.5ng/mL to 6.5ng/mL ($P<0.0001$). There were no episodes of AR. There was decreased inter and intra-patient variability.
91	Florman	2007	2 year post conversions data for Florman 2005. Multi-center observational study.	56	TAC QD	The mean conversion ratio was 0.71. The AUC was similar. Max concentration and fluctuations significant reduced. One patient discontinued QD (unrelated to the drug) during the core study and 3 discontinued during the extension phase. 1 episode of AR occurred during the extension phase. Note the LCP formulation of TAC was used in this study.
92	Sañko-Resmer	2012	Multicenter, open-label, Phase III study, FU 12 weeks	98	TAC BID to QD 1:1	Trough concentration decreased at 1 month but was comparable by 6 months. The majority of patients did not require dose adjustment – the dose increased in 11.4%, 14.3% and 10% of patients at 1, 3, 6 months respectively. Renal function and liver function remained stable.
93	Alloway	2014	Prospective open label, multicenter conversion study, FU 21 days + extension study to 52 weeks)	57 (core study) 43 (extension phase)	TAC BID to QD (LCP-Tacro)	
94	MarinGomez	2009	Observational crossover study, FU 193 days	79	TAC BID to QD 1:1	

Note: Tacrolimus-LCP (veloxis Pharmaceuticals, Hørsholm, Denmark).

Abbreviations: AR, acute rejection; AUC, area under the curve; BID, twice daily; BPAR, biopsy-proven acute rejection; FU, follow-up; LFTs, liver function tests; PK, pharmacokinetic; QD, once daily; TAC, tacrolimus; BP, blood pressure; HBA1c, glycated hemoglobin (A1c); eGFR, estimated glomerular filtration rate; BAAASIS, Basel Assessment of Adherence to medication scale.

Adherence to TAC QD was assessed in four of the 18 studies.^{39,69,82,89} Adherence was improved in three studies^{39,82,89} and was relatively unchanged in one study.⁶⁹ One study measured electronic pill bottle opening and found that both dosing compliance and timing compliance were significantly improved after the conversion ($P=0.008$ and 0.003 , respectively).⁸⁹ The missed-dose rate was twice as high in the TAC BID group.⁸⁹ The beneficial effect on adherence was present in patients converted relatively soon after (6 months to 2 years), during an intermediate period after (2–5 years), and over 5 years after transplantation. Overall, the absolute benefit in adherence with TAC QD was limited since the median compliance level in patients receiving TAC BID was already over 95%.⁸⁹ Subjective quality of life scores were improved in patients taking TAC QD.⁸⁹ Overall, these studies suggest a moderate improvement in already high levels of adherence, but they lack randomized control arms. Furthermore, poorly adherent patients may be underrepresented as recruits to studies of stable patients, so it remains unclear whether TAC QD provides a significant benefit to unstable patients. A causal effect on improved outcomes has not yet been assessed, but may be extrapolated from other studies. Importantly, omitting a dose of a once-daily regimen could be more damaging than omitting a dose of a twice-daily regimen.

Simultaneous pancreas kidney transplantation

One prospective study of 14 de novo simultaneous pancreas kidney patients showed patient, kidney, and pancreas survival at 11 months follow-up of 100%, 100%, and 93%, respectively.³² One pancreas was lost 2 days postoperatively due to vascular graft thrombosis. Interestingly, drug levels declined in weeks 2–3, and the authors commented that patients sometimes required substantial doses and that drug levels responded slowly to dose changes. They suggested that there might be a different pharmacokinetic profile in simultaneous pancreas kidney transplantation due to enteric drainage or improvements in gastroparesis.³² This could be further dissected by analyzing pharmacokinetic data in patients with bladder drainage of exocrine secretions.

Specific effects on glucose metabolism

Tacrolimus causes a dose-dependent decrease in insulin secretion, and some studies have indicated that tacrolimus has a stronger association with new-onset diabetes after transplantation (NODAT) compared to cyclosporine. Since high peak concentrations are associated with impaired glucose metabolism,

there has been interest in whether the pharmacokinetics of TAC QD improve glucose metabolism. Although most conversion studies have not reported any change in glucose metabolism or NODAT, they had not used the gold standard technique for investigating glucose metabolism. A study using the gold standard glucose clamp technique before and after conversion to TAC QD in stable renal transplants did not find any significant change in insulin sensitivity despite reduced tacrolimus peak and trough levels (no difference in AUC was observed).⁵³ The authors concluded that switching to TAC QD was not an evidenced treatment for patients developing NODAT, though they did not study this patient group.⁵³ A specific effect on glucose metabolism was examined in a short 4 week prospective study of 26 patients switching from TAC BID to TAC QD with a 1:1 dose conversion.⁵² Four weeks after conversion, there was an improvement in pancreatic islet beta-cell function and glycated hemoglobin levels.⁵² These effects were considered secondary to reduced trough levels of TAC QD after conversion.⁵² Reduced blood glucose levels were observed in 52 stable renal-transplant patients converted to TAC QD (103.4 mg/dL versus 95 mg/dL, $P<0.03$) in association with reduced trough TAC levels.⁴⁴ A small crossover study with a control group found that TAC QD was associated with improved glucose and triglyceride levels as well as trough drug levels that were nonsignificantly lower after conversion.⁶⁰

Genetic effects on pharmacokinetics

Tacrolimus is metabolized by CYP3A5, a member of the cytochrome P450 superfamily of enzymes. Individuals vary in their expression of functional CYP3A5 protein. The CYP3A5*1 allele results in expression of an mRNA that encodes a functional enzyme, and individuals possessing this allele are termed “expressors”. The CYP3A5* allele results in an mRNA with a premature stop codon, and individuals with these alleles are termed “non-expressors”. TAC QD levels are altered by CYP3A5 expressor status such that the CYP3A5*1/*1 genotype has been associated with trough levels that are 25% lower than those seen with the CYP3A*3/*3 genotype.^{26,28} Homozygotes for the CYP3A5*1 allele had an increased risk of acute rejection ($P=0.01$) in some studies of patients treated with TAC BID.⁹⁵ Future studies may investigate whether genotyping kidney transplant recipients or liver donors alters clinically meaningful outcomes.

Conclusion

Over the last 10 years, tacrolimus has become the most popular CNI for preventing allograft rejection. The availability of

a once-daily form represents has the potential to improve adherence. It is evident from studies lasting up to 2 years in both liver and kidney recipients that TAC QD is broadly equivalent in efficacy and side effects. However, no clear benefits have been demonstrated for hard clinical outcomes and problems such as dose-related effects on insulin secretion remain. Nevertheless, a strong literature exists for the role of nonadherence in graft loss, and modestly improving adherence by concomitantly easing the pill burden could be beneficial. Effects on outcomes arising from improved compliance will require long-term data in large numbers of patients. From a practical perspective, clinicians need to recognize the potential for lower drug levels compared to TAC BID in the first few weeks of starting or converting to TAC QD. For this reason, when converting from TAC BID to TAC QD, consideration should be given to increasing the overall dose by 10%–15%. However, since predictive criteria for interpatient dose responses remain unknown, only careful monitoring can ensure therapeutic levels. There remains a potential concern that, in some studies, trough levels have been persistently lower and could impact on graft function in the long-term, but there may be reciprocal benefits from reduced nephrotoxicity.

Disclosure

The authors report no conflicts of interest in this work.

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