REVIEW

Advagraf®, a once-daily prolonged release tacrolimus formulation, in kidney transplantation: literature review and guidelines from a panel of experts

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SUMMARY

The efficacy and safety of tacrolimus twice-a-day (BID) and once-a-day (QD) formulations are similar. However, the available information regarding the initiation and management of tacrolimus QD is sparse and practical information is lacking. A panel of French experts extensively reviewed the available literature on tacrolimus pharmacokinetics, clinical efficacy, and safety in kidney transplantation and, based on their own day-to-day experience, provided the practitioners with practical guidelines for the daily use and management of tacrolimus QD in *de novo* initiation or early conversion.

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Introduction

Tacrolimus is a keystone immunosuppressive agent used in the prevention of organ rejection following transplantation. The efficacy of the traditional twice-a-day (BID) formulation (Prograf®) after kidney transplantation has been demonstrated in multiple studies [1].

A once-a-day (QD) formulation (Advagraf®) has been approved since 2007 in many countries. The efficacy and safety of both formulations are similar.

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However, the available information related to the initiation and management of tacrolimus QD may be considered as sparse and practical information is lacking.

On the basis of an extended literature review, French experts in kidney transplantation were asked to evaluate the data available on Advagraf®, a QD tacrolimus formulation, and to provide their recommendations, when literature data are lacking, in order to highlight the pharmacokinetic differences between the two formulations and their consequences on therapeutic drug monitoring (TDM), to discuss the prescription modalities of tacrolimus QD in the context of *de novo* initiation or early conversion, and to discuss the advantages and limitations of tacrolimus QD.

The aim of this article is to provide an evidence-based data about the use of tacrolimus QD in kidney transplantation, as well as key information for practitioners for the day-to-day use of this modified release form.

Materials and methods

Following a search of the literature published up to May 2012 and restricted to the approved QD formulation (Advagraf®), a French committee of six experts defined three topics to be discussed: pharmacokinetics, prescription modalities in *de novo* initiation or early conversion, and pros and cons of tacrolimus QD. The experts worked by groups of 2, with the support of an expert in tacrolimus pharmacokinetics, and prepared a briefing document that was thereafter approved by an enlarged board of 10 other French experts. Certain practical guidelines are based on the experts' day-to-day experience and may not be in accordance with the approved labeling of tacrolimus QD.

To provide the most up-to-date data, relevant articles on tacrolimus QD published after the completion of the experts' work have also been reviewed and taken into account in this paper.

Pharmacokinetic differences between tacrolimus QD and BID and impact on TDM

Tacrolimus is characterized by a narrow therapeutic index, a large inter- and intra-individual pharmacokinetic variability, and a better correlation between C_{min} and effects than between dose and effects [2]. The strong correlation between C_{min} and systemic exposure (AUC) allows individualizing the dose by monitoring the C_{min} level as a surrogate marker of exposure [3]. Monitoring C_{min} is mandatory to minimize the risk of rejection (C_{min} below the target range), the risk of nephrotoxicity, and, to a lesser extent, neurotoxicity (C_{min} above the target range) [4,5].

The pharmacokinetic differences between the two formulations come from the difference in excipients: Replacing croscarmellose by ethylcellulose slows down the diffusion rate of tacrolimus, leading to a prolonged release.

Pharmacokinetic comparison in healthy volunteers

Compared with the BID formulation, tacrolimus QD yields similar exposure (AUC), C_{min} and terminal half-life, a reduced peak concentration (C_{max}), and a similar correlation between AUC and C_{min} [1].

As observed with tacrolimus BID, the pharmacokinetic data obtained after a high-fat breakfast showed a 25% decrease in $AUC_{0\text{-}24}$ and C_{max} relative to that in the fasted state. AUC and C_{max} are 17% and 50% lower, respectively, following the evening dose compared with the morning dose when at steady state [6].

Pharmacokinetic comparison in a context of de novo initiation

In comparison with the BID formulation, the QD formulation is associated with a reduction in $AUC_{0\text{-}24}$ on day 1 by approximately 30%, leading to an increase in the dose in order to maintain C_{min} within the target range.

In a phase II study, kidney transplant adults received either tacrolimus QD or BID, in association with mycophenolate mofetil (MMF) and corticosteroids (CS). The initial dose was 0.2 mg/kg/day in both groups; subsequent doses were adjusted to maintain C_{min} in the range of 10–20 ng/ml (days 1–14) and 5–15 ng/ml (day 15 to week 6). The C_{min} values for the two formulations were comparable by day 4 and within the target ranges at each visit. However, this required slightly higher doses of tacrolimus QD than BID (except on week 1). The $AUC_{0\text{-}24}$ was lower for tacrolimus QD than for BID on day 1 at comparable doses (−30% approximately; 232 vs. 361 ng h/ml), but comparable on day 14 (−6%; 364 vs. 384 ng h/ml) and week 6 (−13%; 331 vs. 383 ng h/ml). There was a strong and comparable correlation between C_{min} and $AUC_{0\text{-}24}$ for the two formulations ($r = 0.83$: tacrolimus QD; $r = 0.94$: tacrolimus BID). The authors concluded that the same TDM strategy (in terms of exposure index and target ranges) could be used for both formulations [7]. It is worth noting that C_{min} targeted in phase II studies was in accordance with the SmPCs of tacrolimus QD and BID, which is higher than the level currently used in clinical practice. Results from a recent study conducted in 102 *de novo* kidney transplant recipients and using low

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targets for C_{min} (6–10 ng/ml during the induction phase and 4–6 ng/ml in the maintenance phase) also showed comparable $AUC_{0\text{-}24}$ at day 14 and strong correlation between C_{min} and $AUC_{0\text{-}24}$ for both formulations [8].

In a phase III, noninferiority study in *de novo* kidney transplantation, the mean daily maintenance dose was higher for tacrolimus QD than for BID at all time points (Table 1). The mean C_{min} was significantly lower in tacrolimus QD than in BID group at week 1 (12.8 vs. 15.3 ng/ml; $P < 0.005$), but was comparable thereafter [9]. In a subset of patients, tacrolimus was initiated within 12 h before graft reperfusion (day 0). The $AUC_{0\text{-}24}$ on day 1 was approximately 16% lower for tacrolimus QD than for BID, that is, less than the 30% observed with tacrolimus QD in the phase II study [7], suggesting that initiating therapy before transplant could be a strategy to minimize the difference in exposure on day 1 [10].

The lower C_{min} and/or the need to increase the dose of tacrolimus QD in order to achieve similar C_{min} levels to those obtained with the BID formulation were also observed in retrospective studies [11–13].

However, this lower early exposure with tacrolimus QD was not systematically observed as illustrated in an another phase III, noninferiority study: The mean tacrolimus doses were similar, and C_{min} was variable during the first week for the two formulations. At day 3, the percentage of patients with C_{min} above the target was lower with tacrolimus QD (19%) compared with BID (27.3%) (not statistically significant), whereas the percentage of patients with C_{min} below the target was comparable (30.7% vs. 27.9%, respectively) (Table 1) [14].

Pharmacokinetic comparison in a context of late conversion

A comparable steady-state pharmacokinetics was demonstrated in a prospective, open-label, crossover study in stable kidney transplant patients converted from tacrolimus BID to QD (1:1 mg) at least 6 months after transplantation; the ratios QD/BID of the natural logarithm-transformed pharmacokinetic parameters were as follows: 88.15% (82.7–94.0) for C_{max}; 94.97% (90.7–99.4) for $AUC_{0\text{-}24}$; and 87.2% (82.7–91.9) for C_{min} [15].

A decrease in tacrolimus systemic exposure (approximately 10–15%) was shown following the late conversion from tacrolimus BID to QD (1:1 mg). In a prospective study conducted in kidney transplant recipients converted more than 3 years after transplantation, tacrolimus doses remained stable during the study. However, C_{min} decreased significantly 1 week postconversion (6.8 ± 1.9 ng/ml vs. 7.6 ± 1.8 at baseline), a difference that was maintained at 3 months postconversion (6.4 ± 1.3 ng/ml) ($P < 0.05$) [16]. Stability of tacrolimus doses and a slight decrease in C_{min} (−12%) were also observed in a recent study conducted in 589 patients converted 4.5 years after transplantation [17].

A C_{min} decrease was further confirmed in a recent retrospective study conducted in renal allograft recipients converted 1142 days (6-7848) post-transplantation. After conversion, C_{min} decreased significantly (−1.36 ± 2.51 ng/ml or −12.66% ± 24.36%, $P < 0.0001$); the decrease exceeded 20% in 38.3% of patients and led to a prompt dose increase in 56.1% of them, whereas an increase exceeding 25% was observed in only 4.7% of patients. The dose was increased in 52.5% of patients, the increase being significantly more pronounced in patients switched within the first 3 months after transplantation compared with patients switched later (+1.81 ± 2.96 mg/day vs. +0.40 ± 1.13 mg/day; $P = 0.0011$). Despite dose adjustments, the average C_{min} remained 9.09% ± 28.85% lower after conversion when compared to the corresponding timeframe before conversion ($P < 0.0001$) [18].

Variability in tacrolimus QD exposure

As for tacrolimus BID, a wide inter- and intra-individual variability has been evidenced with tacrolimus QD [19,20].

High inter-individual coefficients of variation (CV) for $AUC_{0\text{-}24}$, C_{min}, C_{max}, and T_{max}, ranging from 45% to 47%, have been reported [4]. Among the numerous factors influencing the pharmacokinetic parameters of tacrolimus (age, race, hepatic dysfunction, albumin concentration, hematocrit, time after transplant, circadian rhythm, food administration, corticosteroid dosage, diarrhea…) [19], the CYP3A5*1/*3 genotype is of particular interest (80–88% of Caucasian population is deficient in this enzyme) [2]. This polymorphism in the gene coding for CYP3A5 may partly explain the wide inter-individual variability. Previous studies demonstrated that recipients carrying at least one CYP3A5*1 allele require higher doses of tacrolimus BID (1.5 times higher) to reach the target C_{min} [2,21]. This was confirmed for tacrolimus QD in a prospective, open-label study conducted in stable kidney transplant recipients converted from tacrolimus BID to QD, where a significant decrease in the dose-standardized $AUC_{0\text{-}24}$ was observed in the study population overall. However, in the CYP3A5 nonexpressor group, the mean C_{min} was comparable for the two formulations, while it decreased significantly after conversion in the expressor group (8.2 ± 2.2 vs.

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Table 1. Summary of the published studies with *de novo* administration of tacrolimus QD in kidney transplant patients [9,14,25]

	Silva *et al.* [14]			Krämer *et al.* [9]		Albano *et al.* (OSAKA study) [25]			
FAS	Tac QD *N* = 214	Tac BID *N* = 212	Neoral *N* = 212	Tac QD *N* = 331	Tac BID *N* = 336	Tac BID 0.2 mg/kg/day *N* = 309	Tac QD 0.2 mg/kg/day *N* = 302	Tac QD 0.3 mg/kg/day *N* = 304	Tac QD 0.2 mg/kg/day + basiliximab *N* = 283
Dose	0.15–0.2 mg/kg/day		8–10 mg/kg	Pre-operative: 0.1 mg/kg/day Postoperative: 0.2 mg/kg/day		Pre-operative: 0.1 mg/kg/day Postoperative: 0.2 mg/kg/day	Pre-operative: 0.1 mg/kg/day Postoperative: 0.2 mg/kg/day	Pre-operative: 0.15 mg/kg/day Postoperative: 0.3 mg/kg/day	Pre-operative: 0.1 mg/kg/day Postoperative: 0.2 mg/kg/day
Target C_{min}	D0-D90: 7–16 ng/ml >D90: 5–15 ng/ml		D0–D90:125–400 ng/ml >D90:100–300 ng/ml	D1–D28: 10–15 ng/ml D29–D168: 5–15 ng/ml >D168: 5–10 ng/ml		D0–D14: 10–15 ng/ml D15–D42: 5–12 ng/ml D43–D168: 5–10 ng/ml			
Induction MMF/CS	Basiliximab MMF + CS			No induction MMF + CS		No induction MMF + CS	No induction MMF + CS	No induction MMF + CS	Basiliximab MMF + CS (day 0 only)
Primary endpoint	Efficacy failure at 1 year [a]			Local BPAR within 24 weeks after transplant (PP data set)		Efficacy failure at week 24 (PP data set)[b]			
Efficacy failure/BPAR rates	14.0%	15.1%	17.0%	20.4%	15.8%	40.6%	42.2%	44.2%	48.2%
Treatment difference [c] (CI) [d]	−3.0% (−9.9; 4.0%)	−1.9% (−8.9; 5.2%)		4.5% (−1.8%; 10.9%)			−1.6% (−12.2%; 9.0%)[e]	−3.5% (−13.6%; 6.6%)[e]	−7.1% (−16.1%; 1.9%)[e]

Tac: tacrolimus; QD: once a day; BID; twice a day; MMF: mycophenolate mofetil; CS: corticosteroid; CI: confidence interval; PP: per protocol; BPAR: biopsy-proven acute rejection FAS: full analysis set.

[a]Composite endpoint: death, graft failure, biopsy-proven acute rejection, or lost to follow-up.

[b]Composite endpoint: graft loss, biopsy-confirmed acute rejection, graft dysfunction.

[c]Noninferiority: prespecified 10% margin for the treatment difference for Silva *et al.* [14] and Krämer *et al.* [9]; 12.5% for Albano *et al.* [25].

[d]95% CI for Krämer *et al.* [9]; Albano *et al.* [25]; 95.2% CI for Silva *et al.* [14].

[e]Noninferiority versus tacrolimus QD 0.2 mg/kg/day.

6.3 ± 2.5 ng/ml; $P = 0.02$). A good correlation between $AUC_{0\text{-}24}$ and C_{min} was observed for both formulations regardless of the CYP3A5 genotype. As expected, the observed $AUC_{0\text{-}24}$ under tacrolimus QD is not double the $AUC_{0\text{-}12}$ under tacrolimus BID [22], because of the circadian rhythm of tacrolimus pharmacokinetics that results in lower $AUC_{0\text{-}12\ h}$ after the evening dose of tacrolimus BID.

A conversion study in stable Taiwanese kidney transplant recipients showed that the intra-individual CV of C_{min} decreased significantly from 14.0 ± 7.5% to 8.5 ± 5.0% ($P < 0.05$), that is, by approximately 40%, after conversion [5]. A recent study in 40 renal transplant patients converted on a 1:1 mg basis confirmed a reduced intra-individual variability in a 24-h exposure for tacrolimus QD compared with BID (10.9% vs. 14.1%; $P = 0.012$), especially among patients expressing CYP3A5 [23].

Therapeutic drug monitoring

In routine practice, TDM is based on C_{min} as a surrogate marker of exposure because of the good correlation existing for both formulations between C_{min} and $AUC_{0\text{-}24}$ [7]. However, a twofold range of $AUC_{0\text{-}24}$ values was found for similar C_{min} values [4], raising doubt about the accuracy of TDM based on C_{min}. As measuring a full AUC based on numerous concentrations is impractical in clinical routine, Bayesian estimators using routinely applicable sampling strategies were developed for optimizing tacrolimus monitoring [2,4,24].

Prescription modalities of tacrolimus QD in *de novo* initiation or early conversion

De novo initiation

Systemic exposure in *de novo* kidney transplant recipients is lower with the QD formulation, especially at the beginning of the treatment, leading to the consideration of dosage adjustment to reach C_{min} targets. The efficacy and safety of *de novo* initiation of tacrolimus QD were evaluated in large clinical studies using fairly similar immunosuppressive protocols (Table 1) [9,14,25].

In a phase III, noninferiority study, *de novo* kidney transplant recipients received either tacrolimus QD, BID, or cyclosporine in combination with MMF, CS, and basiliximab as induction. The primary efficacy endpoint was the efficacy failure rate at 1-year post-transplant (composite endpoint of death, graft loss, BPAR, or lost to follow-up). The efficacy failure rate was comparable between the three groups (14%, 15.1%, and 17% with tacrolimus QD, BID, and cyclosporine, respectively). Both formulations were statistically noninferior to cyclosporine for the primary endpoint (Table 1) [14].

The efficacy and safety of tacrolimus QD and BID combined with MMF and CS (without induction) in *de novo* kidney transplantation were compared in a noninferiority study [9]. Tacrolimus QD did not differ significantly from BID for the BPAR event rate at 24 weeks (primary efficacy endpoint) (20.4% vs. 15.8%; $P = 0.182$). However, the noninferiority of tacrolimus QD versus BID was not achieved as the upper limit of the 95% CI fell just outside the predefined 10% noninferiority margin (treatment difference: 4.5%; 95% CI: −1.8%; 10.9%) (Table 1).

A third noninferiority study compared the two formulations with four arms: tacrolimus BID 0.2 mg/kg/day, and tacrolimus QD 0.2 mg/kg/day or 0.3 mg/kg/day, in combination with MMF and CS, except in one group where tacrolimus QD 0.2 mg/kg/day was associated with basiliximab induction and CS given only perioperatively [25]. The primary efficacy endpoint was the efficacy failure rate at 24-week post-transplant (composite endpoint of graft loss, BPAR, or graft dysfunction). Noninferiority was demonstrated for tacrolimus QD versus BID (same starting dose 0.2 mg/kg/day) for the efficacy failure rate (42.2% vs. 40.6%, respectively) but was not achieved for the higher starting dose of tacrolimus QD 0.3 mg/kg/day vs. BID 0.2 mg/kg/day (44.2% vs. 40.6%, respectively). Noninferiority was also not demonstrated with tacrolimus QD 0.2 mg/kg/day and steroid avoidance (48.2%) (Table 1).

Another randomized, controlled study compared the efficacy and safety of low-dose tacrolimus QD and BID combined with MMF, CS, and basiliximab as induction in *de novo* kidney transplantation. Efficacy profiles of both formulations were similar over the 1-year study period, with overall incidences of BPAR similar to those reported in previous studies (10% for tacrolimus QD; 17.3% for BID; no significant difference) [8].

A recent overview, including all published phase III/IV studies in *de novo* patients, concluded that tacrolimus QD is as effective as BID in preventing acute rejection, graft dysfunction, and graft loss [26].

In daily practice, when tacrolimus QD is initiated *de novo*, we recommend a pre-operative dose of 0.1 mg/kg/day, to avoid potential early underexposure of tacrolimus, followed postoperatively by 0.2 mg/kg/day of tacrolimus QD taken in the morning, under fasting conditions. The same TDM as for tacrolimus BID,

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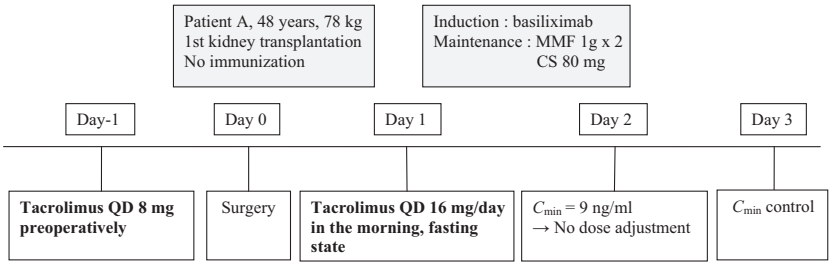

Figure 1 Example of prescription—Tacrolimus QD *de novo*.

based on the same C_{min} target, is recommended. An example of prescription in *de novo* administration is given in Fig. 1.

Early conversion before hospital discharge

Compared with *de novo* initiation, the early conversion from tacrolimus BID to QD may offer several advantages: It is expected to reduce the odds of underexposure with tacrolimus QD in the early period post-transplantation; in addition, delaying the administration of tacrolimus QD would avoid the reduction in absorption because of the postoperative ileus (owing to the more distal intestinal absorption of tacrolimus QD). However, early conversion might induce underexposure at the time of conversion and increase the time interval before the target C_{min} is reached, leading to the prolongation of hospitalization. In addition, there is a paucity of prospective data in the literature regarding the efficacy and safety of the early conversion. A retrospective study comparing tacrolimus BID with early conversion (mean: 12 days post-transplant) to tacrolimus QD showed a similar dosage and C_{min}, as well as the same patient and graft survival, rejection rate, renal function, and safety profile at 1 year [27].

From our point of view, early conversion (1:1 mg) should be performed after bowel movement resumed, at steady state (stable C_{min} within the target range or 10–20% above, usually during the second week; if C_{min} is below the target range, then conversion should be postponed). If after conversion C_{min} decreases by about 10–15% or remains stable, the dosage should not be changed, as the C_{min} decreases more than the $AUC_{0\text{-}24}$ with tacrolimus QD. If a C_{min} decrease >30% is observed, the dosage should be increased. In any case, two consecutive C_{min} measurements should be performed before any dose adjustment. Examples of prescription in early conversion are given in Fig. 2a,b.

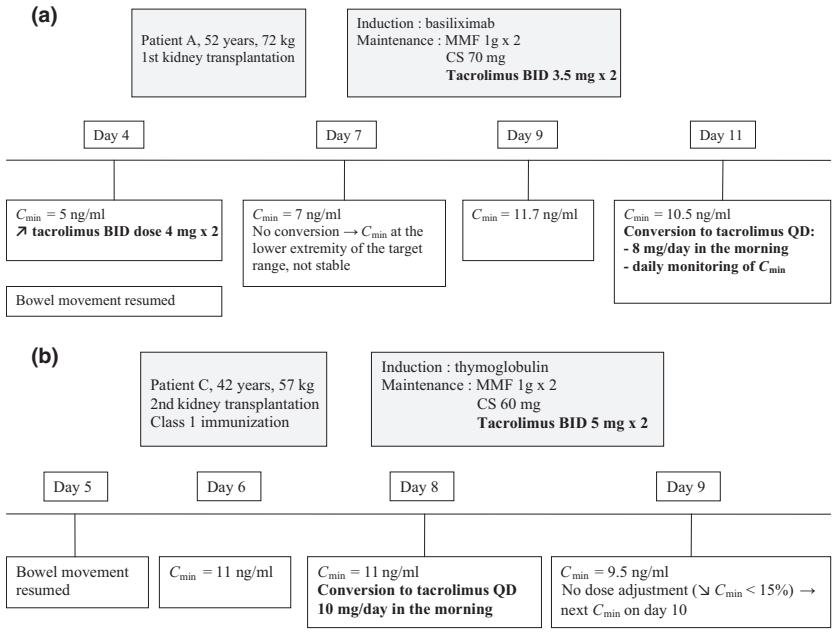

Figure 2 (a) Example of prescription—Early conversion from tacrolimus BID to tacrolimus QD. (b) Example of prescription—Early conversion from tacrolimus BID to tacrolimus QD.

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Advantages and limitations of tacrolimus QD

Adherence to treatment, prevention of acute rejection, and safety profile are key issues for successful immunosuppressive therapy.

Nonadherence is a common and a major cause of transplant failure [28]. The frequency of nonadherence and its impact on kidney graft survival were estimated in a systematic literature review including 15 cross-sectional studies and 10 cohort studies. A median of 22.3% and 15% of patients were "nonadherent" to immunosuppressants in the cross-sectional and cohort studies, respectively. In the cohort studies, a median of 36.4% (13.8–65.2%) of graft losses was associated with prior nonadherence. Meta-analysis of these cohort studies showed that the odds of graft failure increased sevenfold (OR = 7.1; 95% CI: 4.4–11.7%, $P < 0.001$) in nonadherent patients compared with that in adherent patients. The authors concluded that significant improvements in graft survival could be expected from effective interventions to improve adherence [28]. In a meta-analysis of 147 studies including all types of transplantation, nonadherence to immunosuppressive therapy was higher in kidney graft recipients compared with other organ recipients (36 cases/100 persons/year versus 7–15 cases) and appeared weakly correlated with demographics, social support, and perceived health [29]. Similarly, in a prospective cohort study in kidney transplant recipients, demographic, socioeconomic, medical, surgical, and psychosocial characteristics were not associated with adherence. On the contrary, transplant centers and dosing frequency were independently associated with adherence: more frequent dosing schedules were associated with lower adherence (OR = 0.43; 95% CI: 0.22–0.86 for three or four administrations/day; OR = 2.35; 95% CI: 1.01–5.45 for one administration/day versus two administrations/day; $P = 0.003$) [30].

The relation between dosing frequency and adherence was assessed in a randomized, controlled study comparing treatment adherence to tacrolimus BID and QD in 219 stable kidney transplant patients using an electronic device to monitor drug intake. Medication adherence was analyzed by examining how long the patients stayed with the treatment (persistence) and how well the patients implemented the regimen while still engaging to the treatment (implementation). Persistence with the regimen was marginally higher in the once-daily group than in the twice-daily group (81.5% vs. 71.9% respectively at 6 months; $P = 0.0824$). Among patients who remained engaged with the regimen, 88.2% of the once-daily group and 78.8% of the twice-daily group ($P = 0.0009$) took the prescribed number of daily doses [31]. In addition to improved adherence, an observational study showed that after conversion, patients clearly expressed a preference (99.4% of positive feeling) for tacrolimus QD [32].

In addition to adherence improvement, potential advantages in terms of efficacy and safety should be discussed. After *de novo* initiation, the efficacy of both formulations was comparable in terms of patient and graft survival at 12 months in the studies by Silva *et al.* (98.6% and 96.7% for QD; 95.7% and 92.9% for BID, respectively), Krämer *et al.* (96.9% and 91.5% for QD; 97.5% and 92.8% for BID, respectively), and Tsuchiya *et al.* (100% for both formulations) [8,9,14]. In these studies, both formulations showed equally well-maintained renal function at 12 months (Silva *et al.*: MDRD-estimated GFR 58.6 ± 17.64 ml/min/1.73 m² for QD; 59.7 ± 18.24 ml/min/1.73 m² for BID; Krämer *et al.*: creatinine clearance 66.76 ± 21.80 ml/min for QD; 67.10 ± 18.53 ml/min for BID; Tsuchiya *et al.*: eGFR 51.7 ± 15.9 ml/min/1.73 m² for QD; 51.8 ± 18.7 ml/min/1.73 m² for BID) [8,9,14]. In the OSAKA study, patient and graft survival at 24 weeks were also similar (97.3% and 90.4% for tacrolimus QD 0.2 mg/kg/day; 98.0% and 94.1% for tacrolimus BID 0.2 mg/kg/day, respectively). Kidney function at 24 weeks was similar, except in the steroid avoidance arm: MDRD-estimated GFR: 45.7 ml/min/1.73 m² (tacrolimus QD 0.2 mg/kg/day); 45.9 ml/min/1.73 m² (tacrolimus QD 0.3 mg/kg/day); 41.7 ml/min/1.73 m² (tacrolimus QD 0.2 mg/kg/day, steroid avoidance); and 48.3 ml/min/1.73 m² (tacrolimus BID 0.2 mg/kg/day) [25].

In these *de novo* studies, the comparative safety profile of both formulations was not always consistent. Specifically, the incidence of infections was similar in Silva and Tsuchiya *et al.*'s studies [8,14], whereas a higher incidence of cytomegalovirus infections (10.0% vs. 5.7%; $P = 0.043$) and bacterial pyelonephritis (3.6% vs. 0.9%; $P = 0.019$) and a lower incidence of bacterial infections (16% vs. 22.6%; $P = 0.032$) were reported with tacrolimus QD in Krämer *et al.*'s study [9].

Development of new-onset diabetes is a major clinical concern following kidney transplantation. There was no statistically significant difference in the incidence of diabetes mellitus and hyperglycemic conditions between the two formulations in Krämer and Tsuchiya *et al.*'s studies [8,9]. In Silva *et al.*'s study [14], the incidence of new-onset diabetes was even

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slightly lower with tacrolimus QD (56.4% vs. 64.0%), and the incidence of insulin use was comparable (5.5% vs. 6.0%), while oral hypoglycemic agents were more often used (14.1% vs. 10.0%) (no statistical comparisons performed).

Renal function was evaluated in a large prospective study including 1832 stable kidney transplant recipients converted 1838 ± 1450 days after transplantation from tacrolimus BID to QD. A statistically significant, but not clinically relevant increase in serum creatinine was observed from 127.7 μmol/l at conversion to 133.3 μmol/l 12 months after conversion. However, the mean GFR did not change significantly (56.46 ± 19.7 ml/min at conversion versus 55.7 ± 20.6 ml/min at 12 months). In addition, no significant changes were observed in other clinical and biochemical parameters at the end of study, and the rate of BPAR was low (0.4%) [32].

In a retrospective cohort study in 72 kidney or pancreas–kidney transplant recipients, converted 43 months after transplantation, generally on a 1:1 mg basis, the kidney graft function improved: There was a decrease in serum creatinine (approximately −9%) within the 12 months after conversion and an increase in estimated GFR (+15.6%) 24 months after conversion. A concomitant decrease in C_{min} was observed, but no significant correlation between the increase in estimated GFR and C_{min} decrease was found [33]. Similar results were obtained in a prospective study in 31 kidney transplant recipients converted 45.4 ± 22 months after transplantation (1:1 mg): C_{min} showed a slight but significant reduction after conversion (5.7 vs. 5.1 ng/ml; $P = 0.024$) and significant improvements in creatinine levels (1.6 vs. 1.5 mg/dl; $P = 0.014$) and MDRD-estimated GFR (53.4 vs. 55.4 ml/min; $P = 0.016$). As in Kolonko *et al.*'s study [33], no significant correlation was found between the reduced C_{min} and the improved renal function [34].

Conversion has no deleterious effect on metabolic parameters. No relevant differences between the two formulations regarding insulin secretion and insulin sensitivity were observed in a prospective crossover study in 20 stable nondiabetic renal transplant recipients, in spite of the reduced tacrolimus exposure [35].

Conclusion

This extensive literature review along with practical guidelines provides answers to some of the questions the practitioners may have regarding the daily use and management of the QD formulation of tacrolimus (Advagraf®), in *de novo* initiation or early conversion.

Following *de novo* initiation, tacrolimus systemic exposure is reduced by approximately 30% with the QD formulation. This reduction is lower if the first dose is given pre-operatively. Following conversion, a slight decrease (10–15%) in C_{min} is observed, which does not translate into an equivalent decrease in global exposure (AUC).

Intrapatient variability in trough levels appears to be lower with tacrolimus QD. However, a close monitoring of C_{min} levels, or Bayesian estimation of the AUC when needed, is mandatory because of the high interindividual variability in tacrolimus pharmacokinetics. In routine practice, because of a similar, strong correlation between C_{min} and AUC for both formulations, TDM should be based on C_{min} as a surrogate marker of exposure as for the BID formulation, keeping in mind that slightly lower values are generally obtained with the QD formulation.

The efficacy and safety data of tacrolimus QD after *de novo* initiation was extensively evaluated in large populations of patients using fairly similar immunosuppressive protocols. If some studies found an increase in BPAR with tacrolimus QD, it does not translate into a decrease in kidney function or graft survival, which are similar for both formulations. Similar results were observed for both formulations in terms of patient survival, graft survival, renal function, and occurrence of adverse events. In *de novo* initiation, we recommend a pre-operative dose of tacrolimus QD to avoid the early underexposure of tacrolimus.

Although fewer data are available about early conversion before hospital discharge, this option seems to be safe and efficient. If it is chosen, we recommend performing the conversion after bowel movement resumed, at steady state, using a 1:1 mg schedule.

Finally, there is a trend for improved adherence with QD formulation that needs to be confirmed in further clinical studies.

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Conflicts of interest

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*for these three studies (references 25, 27 and 31), data were preliminary extracted from the documentation available at the time of the review, that is, from abstracts (ATC2011-11th Joint Annual Meeting of the American Society of Transplant Surgeons and the American Society of Transplantation, April 30–May 4, 2011, Philadelphia, PA, USA; ATC2012-12th Joint Annual Meeting of the American Society of Transplant Surgeons and the American Society of Transplantation, June 2–6, 2012, Boston, PH, USA; and ESOT2011-15th Congress of the European Society for Organ Transplantation, September 4–7, 2011, Glasgow, UK, respectively). References to the full papers subsequently published are provided in order to provide the most accurate information to the reader.

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