Improved Adherence to Tacrolimus Once-Daily Formulation in Renal Recipients: A Randomized Controlled Trial Using Electronic Monitoring

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Background. With effective agents available to prevent posttransplantation acute organ rejection, medication adherence becomes a key factor for successful treatment outcomes after renal transplantation. A once-daily, modified-release oral formulation of tacrolimus has been developed to simplify dosing and improve medication adherence.
Methods. Adherence Measurement in Stable Renal Transplant Patients Following Conversion From Prograft to Advagraf is a randomized multicenter controlled trial to evaluate adherence between a tacrolimus once-daily regimen and a tacrolimus twice-daily regimen using an electronic monitor to document drug intake. After enrolment, all patients continued the twice-daily regimen for 3 months and then were randomized 2:1 between the two formulations and followed for 6 months. Adherence was decomposed into patients' persistence and implementation of each regimen.
Results. Two hundred nineteen patients (45% male; 3±2 years after transplantation) were analyzed (145 once daily and 74 twice daily). At 6 months after randomization, 81.5% of the once-daily group and 71.9% of the twice-daily group remained persistent with the treatment (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. When the patients took the twice-daily regimen, the average percentage of missed doses was 11.7% in the morning and 14.2% in the evening (P=0.0035).
Conclusions. Regimen implementation of tacrolimus once daily is significantly superior to the twice-daily regimen. There was a residual prevalence of suboptimal adherence that will have to be countered by means other than reformulation and regimen simplification. Electronically compiled dosing histories provide detailed data on patient adherence that can be used for efficient medication management.

Keywords: Medical adherence, Tacrolimus, Regimen simplification, Electronic monitoring, Renal transplantation.

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With effective agents available to prevent posttransplantation acute organ rejection, medication adherence becomes a key factor for successful treatment outcomes

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after renal transplantation. Suboptimal adherence to the immunosuppressive regimen causes a higher risk of late acute rejection and allograft loss (*1–9*). A meta-analysis found that nonadherence to immunosuppressants was highest in renal recipients (*10*).

Evidence from many fields of ambulatory pharmacotherapy shows that less frequent dosing regimen leads to higher percentage of prescribed doses taken (*11, 12*). A once-daily, modified-release oral dosage form of tacrolimus has been developed to simplify dosing and improve medication adherence in ambulatory posttransplant patients. The safety, efficacy, and tolerability of the once-daily, modified-release tacrolimus have been described in several studies (*13–17*). Pharmacokinetic studies have demonstrated that patients can be converted from twice-daily to once-daily tacrolimus formulations on a one-to-one total daily dose basis (*18–20*).

The primary objective of the Adherence Measurement in Stable Renal Transplant Patients Following Conversion From Prograft to Advagraf (ADMIRAD) study is to compare medication adherence between modified-release tacrolimus once-daily and twice-daily regimens. The positive impact of regimen simplification of immunosuppressive drugs to prescribed dose taken has been confirmed in renal transplant recipients (*9*). The superiority of adherence to tacrolimus once daily relative to that of the conventional twice-daily regimen has been suggested in other studies (*13, 21*), yet this has not been tested in a randomized controlled trial. ADMIRAD was the first randomized controlled study to compare medication adherence between tacrolimus once-daily and twice-daily regimens using electronic monitoring.

Electronically compiled drug dosing histories of treated patients provide richly sampled and reliable objective data on patient adherence to the medication (*22*). As each dosing time and date are automatically recorded electronically, the collected data provide accurate times of intervals between successive doses, from the first dose taken to the last dose taken.

RESULTS

From October 2008 to September 2009, 252 patients were enrolled in the ADMIRAD study at six clinical sites across Belgium. After 3 months of baseline adherence evaluation, 219 patients (87%) were randomized: 145 patients were allocated to the once-daily regimen and 74 patients were allocated to the twice-daily regimen. Of the patients allocated to the once-daily regimen, 43% of them were female, 11% of them had a second transplantation, and the randomization occurred on average 3.1±2.0 years since their last renal transplantation. Of the patients allocated to the twice-daily regimen, 38% of them were female, 11% of them had a second transplantation, and the randomization occurred on average 2.9±2.1 years since their last renal transplantation.

Figure 1 describes the study flow diagram. Among the randomized patients, 14 (9.7%) from the once-daily group and 8 (10.8%) from the twice-daily group withdrew earlier than the end of the study period. No patient had an acute rejection during the study. The last patient's last visit occurred in July 2010. Different adherence patterns were observed among the patients in this study (Fig. 2). From the collected patients' dosing history data, we analyzed adherence to both regimens by distinguishing patients' persistence (how long the patients stayed with the treatment) and implementation (how well the patients implemented the regimen while still engaging to the treatment) of the regimens (*23*).

Patients' Persistence With the Medication

Patients' persistence with the medication, described as the percentage of patients who remained engaged with the regimen over the study period, is shown in Figure 3. Persistence with the regimen was marginally higher in the once-daily group than in the twice-daily group (P=0.0824, log-rank test). At 6 months after randomization, 81.5% of the once-daily group and 71.9% of the twice-daily group were still engaged with the treatment. At the time of randomization, the percentage decrease of the once-daily and twice-daily groups are estimated to be 5.5% and 6.8%, respectively. This sudden drop at randomization occurred in both groups, indicating that some patients decided to discontinue participation in the trial immediately after being allocated to each group.

Patients' Implementation of the Dosing Regimen

Patients' implementation of the dosing regimen is analyzed by evaluating the day-by-day percentage of patients with correct dosing of each regimen over the study period (Fig. 4). The percentage calculation was based on the patients who were still engaged to the treatment (persistent) at the time in question, adjusting for the effect of nonpersistence with the regimen. After randomization, implementation was significantly better in the once-daily group compared with the twice-daily group (P=0.0009, generalized estimating equation [GEE] model). The estimated difference between the two curves is 9.8% (88.2% once daily vs. 78.8% twice daily). Time (days since randomization) is not a significant variable in the model (P=0.9765). The difference between prerandomization and postrandomization implementation (82.2% pre vs. 88.2% post) is significant for the once-daily group (P<0.0001) and not significant for the twice-daily group (79.5% pre vs. 78.8% post; P=0.7871). The proportion of patients having at least one single skipped twice-daily dose per month is 84%. The proportion of patients having at least 1-day interval without a dose per month (missing a single dose for once-daily regimen or missing two consecutive doses for twice-daily regimen) is 62% for the once-daily group and 40% for twice-daily group.

The adherence assessment without adjusting for the effect of nonpersistence (see **Figure S1, SDC,** http://links.lww.com/TP/A725) shows that the percentage of patients with correct dosing after randomization was higher in the once-daily group compared with the twice-daily group (P=0.0026, GEE model).

Timing adherence assessment, described by day-to-day percentage of patients who dosed consistently within 2 hr of their respective average intake time (see **Figure S2, SDC,** http://links.lww.com/TP/A725) shows higher percentage of patients who dosed timely after randomization in the once-daily group compared with the twice-daily group (83.7% once daily vs. 73.4% twice daily; P=0.0015, GEE model).

The percentages of missed doses by days of the week and by the time of the day for patients prescribed the twice-daily regimen are described in Figure 5. Saturday's percent of missed doses was significantly higher than that of the other days (P=0.0285), whereas Sunday's percent of missed doses

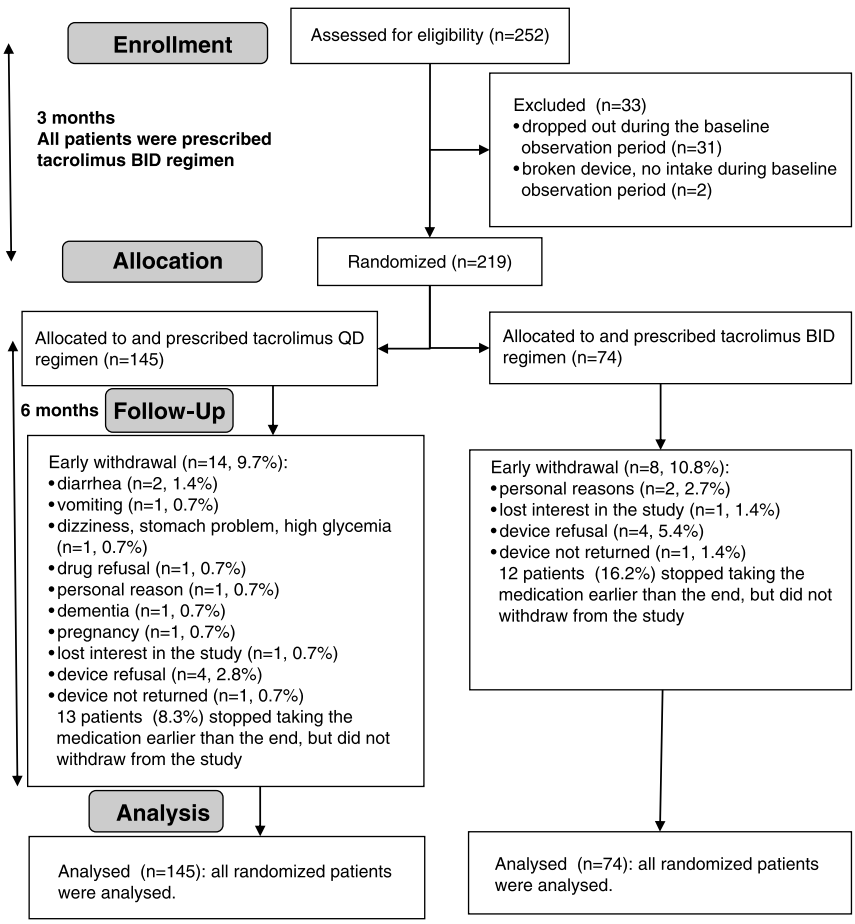

FIGURE 1. Study flow diagram.

was significantly lower that of the other days (P=0.0276). Saturday evening was the time within the week with the most dose omissions (15.6%). The average percentage of missed doses is 11.7% in the morning and 14.2% in the evening (P=0.0035). The percentage of missed doses was significantly higher (P<0.05) in the evening than in the morning for each day of the week, except for Wednesday (P=0.1245).

The average number of dose adjustments after randomization was significantly higher in the once-daily group than in the twice-daily group (1.7 once daily vs. 1.0 twice daily; P=0.0092). The average total number of tacrolimus concentration measurements per patient after randomization was marginally higher in the once-daily group than in the twice-daily group (3.8 once daily vs. 3.4 twice daily; P=0.0901). The difference of the number of concentration measurements between the two groups occurred in the first 2 weeks after randomization (0.7 once daily vs. 0.3 twice daily; P<0.0001). After 2 weeks, the number of measurements is equivalent between the two groups (3.1 once daily vs. 3.1 twice daily; P=0.5743). The average tacrolimus concentrations in the once-daily and twice-daily groups were 7.2 and 8.1 ng/L (P=0.0004), with between-subject standard deviations of 1.8 and 1.9 ng/L (P=0.8672; see **Figure S3, SDC,** http://links.lww.com/TP/A725). The within-subject standard deviations of tacrolimus concentrations in the once-daily and twice-daily groups were 2.1 and 2.5 ng/L (P=0.0911).

DISCUSSION

This study has demonstrated superior implementation of the tacrolimus once-daily regimen over the twice-daily regimen. Improvement of regimen implementation took place after the twice-daily to once-daily regimen switch because the burden of the patient to take an additional dose each day was eliminated. Moreover, the regimen simplification eliminates evening doses that pose higher incidence of missed doses relative to morning doses in the twice-daily regimen. An example of a dosing history of a patient who benefits from a regimen switch from the twice-daily to the once-daily regimen is illustrated in Figure 2 (v). Taking evening doses in the twice-daily regimen was a burden for this patient. Patients' morning activities are relatively more structured than the evening ones, making it easier to associate dose intakes to certain habits or rituals. A similar conclusion has been demonstrated for hypertensive patients treated with a once-daily regimen; patients who took their dose in the morning have less chance to miss their dose relative to those who took their dose in the evening (*24*).

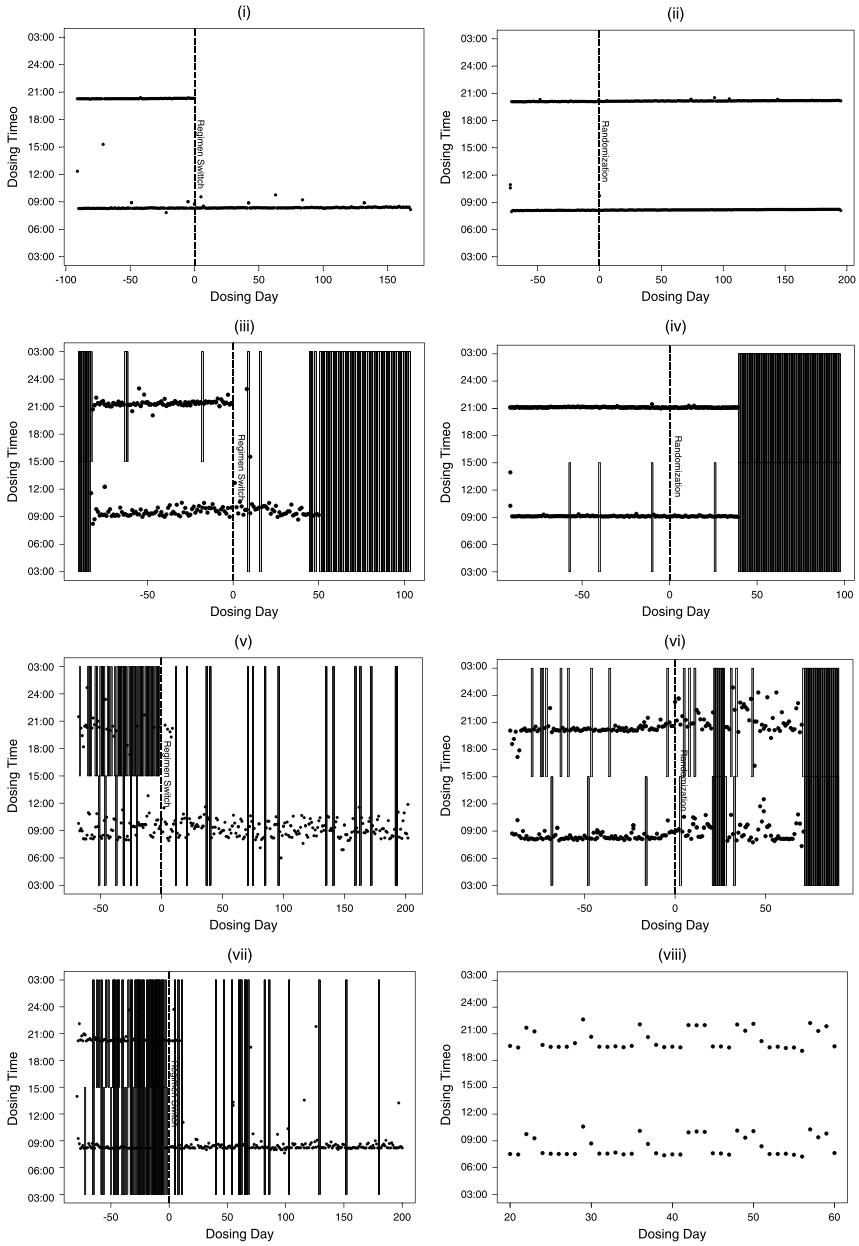

FIGURE 2. Examples of patient's individual plots of drug intake. The horizontal axis displays the dosing dates relative to randomization (time 0). The vertical axis gives the time of drug intake on a 24-hr clock (dosing time) from 3.00 to 2.59 a.m. Each point corresponds to a blister removal from the container. The gray bars correspond to the missed doses. (*Left*) examples taken from patients with once-daily regimen after randomization; (*right*) examples taken from patients with twice-daily regimen after randomization. i and ii, patients with perfect dosing who took their doses at the same time every day. iii and iv, patients with short persistence who stop taking the medication earlier than prescribed. v and vii, patients who had better adherence after regimen switch from twice daily to once daily. vi, a patient who had a worsened regimen implementation before quitting the regimen. viii, a dosing history snapshot of a patient who took the medication at a later time of the day during weekends.

Although the proportion of correct dosing for the once-daily regimen is higher than the one for the twice-daily regimen, the results of this comparison should be cautiously interpreted. It is generally true that a patient prescribed a twice-daily regimen will be more likely to miss a dose than a patient prescribed a once-daily regimen, because twice as many doses are prescribed every day for the twice-daily regimen than for the once-daily regimen. However, the frequency of having at least 1-day interval without dose is higher in the once-daily regimen than in the twice-daily

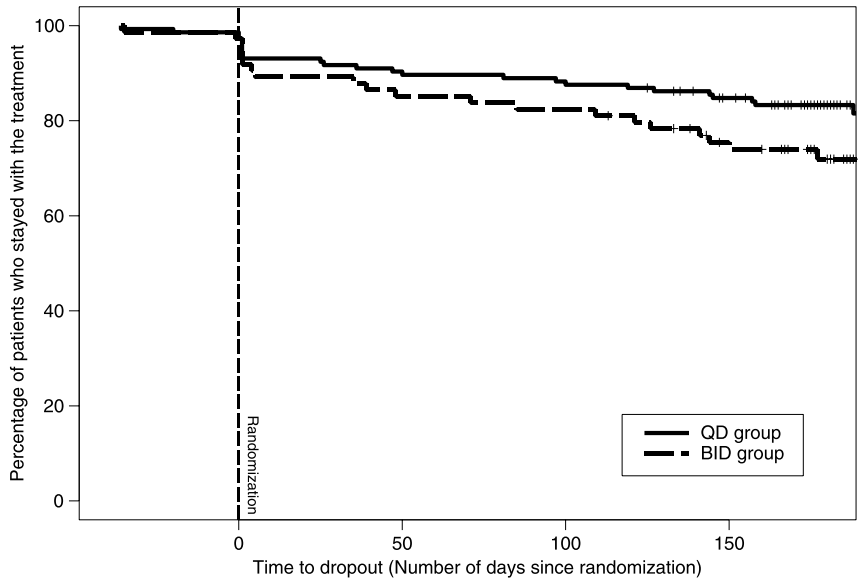

FIGURE 3. Kaplan-Meier estimates of the percentage of patients continuing with the treatment over time. Each small vertical tick mark indicates that a patient was censored in the calculation as he/she completed the study.

regimen. It is therefore important to investigate the pharmacologic effect of each type of dosing error. If the pharmacologic effect from skipping a single twice-daily dose is appreciably less than that from skipping a single once-daily dose, then whereas some patients (e.g., Fig. 2, v) would benefit from a once-daily dosing, other patients who maintain the frequencies of skipped doses after a conversion from twice-daily to once-daily dosing might be better served by a twice-daily regimen. The pharmacologic comparison based on both patients' adherence and pharmacokinetic/pharmacodynamic characteristics of tacrolimus is beyond the scope of this project and should constitute the basis for further research.

Persistence was higher with the once-daily regimen, but the difference was not significant. One possible explanation of this slight difference is that the patients in the

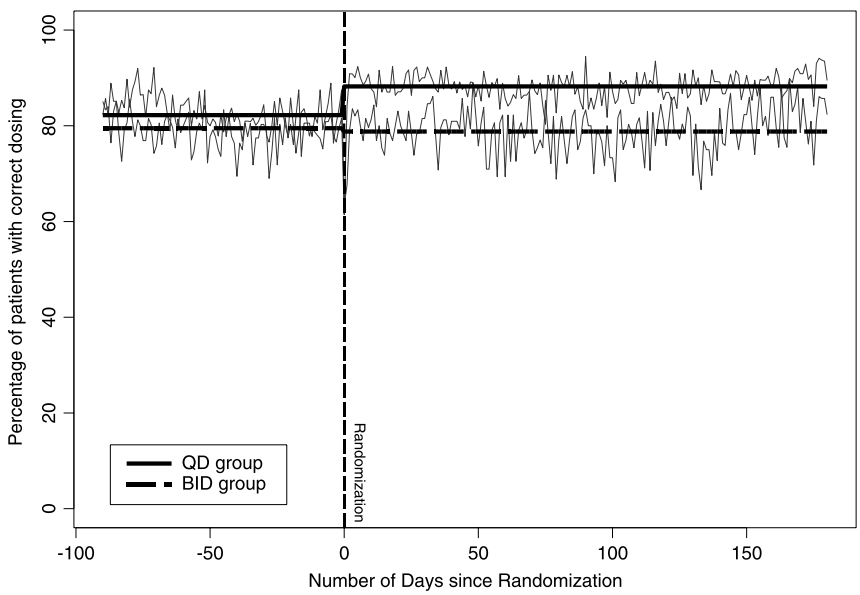

FIGURE 4. The implementation of each dosing regimen represented by the day-to-day percentage of patients with correct dosing relative to patients who were still engaged with the treatment. Correct dosing is defined when the number of the medication intake that day is at least as prescribed. Broken vertical line at time 0 represents time of randomization. The overlaying lines are model-based estimation of the day-to-day percentages.

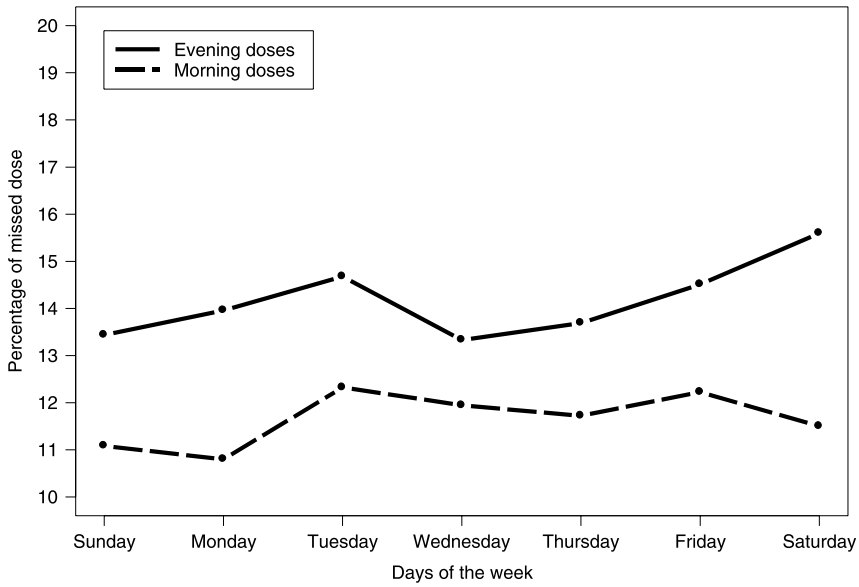

FIGURE 5. Percentage of missed doses by days of the week and morning/evening doses when the patients were prescribed the twice-daily regimen and were still engaged to the treatment.

once-daily group had more tacrolimus concentration measurements and dose adjustment relative to the patients in the twice-daily group; therefore, they had more clinic visits and attention paid to their ongoing implementation of the dosing regimen. This effect is especially prominent early after the randomization. Clinic visit frequency has been shown to have a positive effect on the persistence with treatment (*25*).

This study has certain limitations. As it was intended primarily to evaluate objectively the adherence to tacrolimus once-daily and twice-daily regimens, it did not provide any further information on the link between the adherence data and clinical outcomes. To do this comparison, a longer follow-up with a greater number of patients would be needed, which was beyond the scope of this project. The study design was chosen to be simple and as close as possible to daily practice, resulting a limited list of patients' demographic characteristics, only the ones relevant to the patients' eligibility criteria. Bias in adherence to the patients' demographic factors was assumed to be minimal in this randomized clinical trial.

This study shows that more dose adjustments were needed shortly after the conversion from twice-daily to once-daily regimen. Other studies (*26–28*) confirm the need for dose adjustment of the once-daily regimen in the short term to get the effective therapeutic levels. The mean concentration was significantly lower in the once-daily regimen than in the twice-daily regimen, as reported in other studies (*29, 30*); however, the difference was small and was not reflected in acute rejection.

As transplant recipients are often prescribed multiple immunosuppressants and other medications, setting up an optimal combination therapy would require extra attention to the possible clinically relevant drug interactions (*31*). Intensive monitoring of drug concentrations and adequate dosing responses are not only necessary for either tacrolimus once daily or twice daily but also necessary for all concomitant drugs that require therapeutic drug monitoring. The choice of immunosuppressive regimen should be adapted to ensure optimal clinical outcome.

Detailed and objective patients' dosing history data were valuable in this study in identifying specific patterns of nonadherence, such as missed evening doses or delayed weekend doses. They have provided insight into how patients can benefit from a regimen simplification. There was, however, a residual prevalence of suboptimal adherence that will have to be countered by means other than reformulation and regimen simplification. Electronically compiled dosing histories can be used as feedback to the patients on how well they implement their treatment in clinical practice (*32*). It sets the stage for focused dialogue between healthcare providers and their patients, increasing the quality of the management time spent. Effective medication management, when guided by reliable, current dosing history data, can enhance the daily implementation of, and long persistence with, the prescribed drug dosing regimen (*33, 34*).

MATERIALS AND METHODS

Study Design

ADMIRAD was a randomized, controlled, open-label, multicenter trial conducted in Belgium, with the primary objective of comparing the medication adherence between patients treated with tacrolimus once-daily regimen and the conventional twice-daily regimen. The study was designed and implemented in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, the local regulatory requirements, and the approval of the local medical ethics committee. All patients were provided with a written informed consent document, which each patient signed.

Adult renal transplant patients, treated with tacrolimus twice daily for at least 3 months before inclusion, were included in this study. The patients had to have had their first or second renal transplantation between 6 months and 6 years before the time of inclusion and to have stable health status at the time they entered the trial.

After enrolment, all patients continued the twice-daily regimen for a further 3 months to collect baseline adherence data (run-in period). Patients collected their prescribed tacrolimus in their usual local pharmacy. During the entire study, patients' medication intakes were electronically monitored using the Helping Hand (Bang & Olufsen Medicom, Struer, Denmark) (*35*). At enrolment, trained staff at the clinical sites provided instructions on how to use the electronic monitor. The electronic monitor recorded the time and the date when the blister was reinserted in the monitor. Only tacrolimus medication intakes were monitored in this study. The rationale to have a 3-month run-in period is also to eliminate the potential modification of adherence behavior due to monitoring.

Patients were asked to come for a clinical visit 3 months after inclusion. At this visit, patients were randomized by the investigator or staff at the clinical sites on a 2:1 basis (once daily/twice daily) for another 6 months of follow-up and thus converted either to the once-daily regimen or to continue with the original twice-daily regimen. The randomization sequence was computer generated and centrally done with a block of size 3 stratified by the clinical sites. Patients were asked to come for clinical visit 3 and 6 months after randomization (end of study visit). At each visit, any biopsy-proven or cellular acute rejection events and trough level measurements were reported. The adherence data stored in the electronic monitors were downloaded at each visit during the study period. During these visits, the patients did not receive any additional information that might have influenced their adherence. The patients, the investigators, and their staff had no access to the dosing history data during the study period. The number of dose adjustments between visits was recorded during the period after randomization. In cases of early withdrawal from the study, the time and the reasons of withdrawal were recorded.

Statistical Analysis

The primary endpoint of this study was a comparison of postrandomization adherence to the once-daily and twice-daily regimens. The secondary endpoints included comparison between prerandomization and postrandomization adherence to the regimen for each group, comparison of within-subject variability of tacrolimus concentration, acute rejection rate, and number of dose adaptations between the two groups. 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). If on a given day, the medication was not taken, there can be two reasons: (a) the patient had previously discontinued treatment (nonpersistence) or (b) the patient was still engaged with the dosing regimen but neglected to take a dose on that particular day (nonimplementation).

Persistence is defined as the time from the first taken dose to the last taken dose. The Kaplan-Meier method was used to estimate the percentage of patients who remain engaged with the regimen over time. The log-rank test was used to evaluate if there was any significant difference in the persistence between the two regimens.

The implementation of each dosing regimen is assessed by evaluating the day-to-day percentage of patients who dosed at least as prescribed among patients who were still engaged with the treatment. When a patient stopped taking the medication, then from the day of discontinuation onward, this patient was censored in the percentage calculation. Longitudinal logistic models (*36*) were used to evaluate the implementation of the two dosing regimens. The dependence among observations from a given patient over time is taken into account by GEE models, with a first-order autoregressive covariance structure. The dependent variable is the longitudinal binary variable, indicating whether the patient took a given day's prescribed dose or not. The explanatory variables used were the group indicator, the prerandomization versus postrandomization indicator, and the number of days since the start of the monitoring. The interaction between these variables was assessed in the models.

The sample size of the trial was determined based on the longitudinal logistic model to evaluate medication adherence, with a 5% significance level, 80% power, and 0.20 intracluster correlation. In a previous publication (*37*), the average daily proportion of correct dosing for twice daily was estimated to be approximately 70%. This study was powered to detect a 10% increase in adherence to the simplified once-daily regimen.

A mixed-effects model was used to compare the between- and within-subject variability of the tacrolimus concentrations. All statistical tests were performed two-sided at a 5% level of significance. All randomized patients were included in the analysis on an intention-to-treat basis. When a patient stopped taking the medication or dropped out from the study after randomization, then this patient was considered as nonpersistent in the analysis of persistence and included in the analysis of implementation of the regimen up to the day of discontinuation.

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