A Prospective Randomized Trial on the Effect of Using an Electronic Monitoring Drug Dispensing Device to Improve Adherence and Compliance

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Background. Outcome after renal transplantation depends on patient compliance and adherence for early detection of complications and identification of intervention opportunities. Compliance describes the degree to which patients follow medical advice and take their medications. Adherence has been defined as the extent to which a patients' behavior coincides with clinical prescriptions. **Materials and Methods.** Patients were randomized 7 to 14 days after transplantation into groups with (n = 40) and without (n = 40) an electronic medication dispenser (EMD). The EMD, which was used for the 1-year study period, recorded the date and time the patient took their medications and was monitored via a web-based application. Patients were monitored for 1 year regarding outpatient follow-up visits, emergency hospitalizations, renal biopsies, rejection episodes, renal function, and blood concentration of medications. **Results.** Compliance in the intervention group was 97.8% (the control group was not assessed). Number of missed doses varied significantly by weekday (P = 0.033); patients were most likely to miss doses on Saturdays and Thursdays. Patients missed a total of 11 follow-up visits. During the study, 92 biopsies were performed on 55 patients (intervention group: 32 [17]; control group, 60 [38]). Biopsy-verified rejection was three times more common among controls (13 patients vs 4; P = 0.054, not significant). Average P-creatinine level was slightly lower in the intervention group than the control group (131 vs 150 µmol/L, not significant), whereas mean tacrolimus was similar (7.32 vs 7.22 ng/mL, n.s.). **Conclusions.** The EMD is associated with high compliance, and there are also indications of a lower rejection rate.

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All patients undergoing renal transplant at Karolinska University Hospital are carefully informed about the importance of taking immunosuppressive medications continuously for the life of the graft. During the discharge conference on the ward, the nurse/doctor underscores that the risk of rejection increases if patients do not take their prescribed medication regularly for any reason.

Despite such carefully repeated information, some patients do not take their medications as prescribed. Noncompliance is one of the most common causes of graft loss, and the cost of noncompliance after organ transplantation is estimated to be substantial.[1-3] Such costs may involve treatment for rejection, loss of transplant function, and resumption of dialysis.

The reasons why patients do not take their medications vary from individual to individual.

Some patients may be involuntarily forgetful, but we cannot rule out the possibility that some patients may choose, more or less deliberately, to skip and/or reduce their medication doses.

Involuntary forgetfulness might be associated with distractions, occasional changes in daily routines, or other such factors. The intervention in this study is intended to address involuntary forgetfulness.

Medical psychology has a long tradition of adherence research, highlighting the importance of many psychosocial factors that influence adherence behavior.[4,5] In addition, the World Health Organization has developed a model of the various multifactorial factors contributing to adherence behavior, including health system, organizational, and treatment-related factors.[6] Compliance among transplant patients is inadequately studied in Sweden and the Nordic countries. A survey conducted among more than 1 100 Swedish renal transplant patients showed that over half of the patients stated that they sometimes or rarely forgot to take their medications, whereas 5% often forgot to do so. The majority of patients found it most difficult to remember to take their evening dose. One in 10 said that they sometimes or rarely chose to skip or adjust the medicine dose without consulting their doctor.[7]

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A compliance study from the United Kingdom suggests that noncompliance among teenagers is greater than what was previously thought.[8] The results showed that 15% to 55% of teenagers were noncompliant, and the highest prevalence was observed among renal transplant patients. As time passed after renal transplantation, the risk of noncompliance grew. The teenagers often had brief periods when they forgot to take their medicine, and 15% to 30% of them deliberately chose not to take their medicine during a period known as a "drug holiday." Some stopped taking their medications completely.

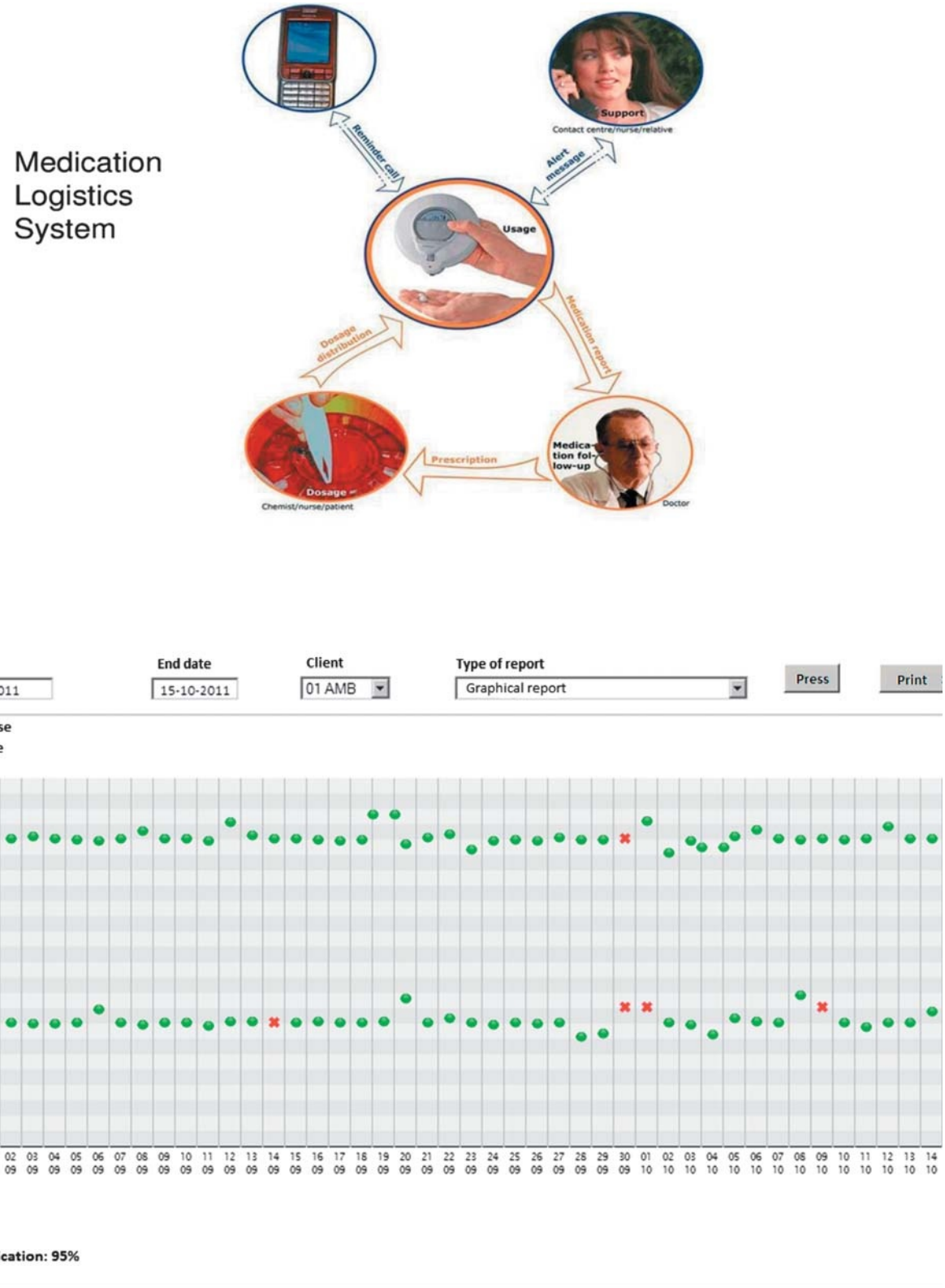

FIGURE 1. Illustration of an EMD with GSM function and web-based software. GSM indicates Global System for Mobile Communications. Figure printed with permission of Addoz Oy. Copyright 2015.

TABLE 1.

Distribution of study participants' immunosuppressant treatment

Intervention group, no. participants				
Prograf + MMF + pred	Prograf + AZA + pred	Advagraf + MMF + pred	Advagraf + MMF	Sandimmun + MMF + pred
19	4	5	10	1
Control group, number of participants				
Prograf + MMF + pred	Prograf + AZA + pred	Advagraf + MMF + pred	Advagraf + MMF	Sandimmun + MMF + pred
23	8	3	6	0

MMF indicates mycophenolate mofetil; AZA, azathioprine; pred, prednisolone

Studies from Belgium report similar prevalence figures, showing noncompliance among teenagers to be over 50%.[5,9]

Patients who experience graft failure also experience lowered quality of life and expected survival; moreover, retransplantation may be complicated by the development of human leukocyte antigen antibodies.[10,11]

The general aim of this study was to study compliance and evaluate the use of an electronic medication dispenser (EMD). We thus chose to conduct a prospective, randomized study in which an EMD with cellular capabilities (tracking device via Global System for Mobile Communications; Figure 1) was evaluated in patients after renal transplantation. The primary aim was to use the EMD to study patient compliance with immunosuppressive medications. A secondary aim was to follow the postoperative course regarding outpatient follow-up visits, emergency readmissions, biopsies, rejection, renal function, and blood concentration of immunosuppressive medication. Other studies have generated important information on the use of EMDs.[12,13] Our hope was to learn more about the extent of noncompliance with the use of an EMD in kidney transplant patients and to study the influence of the EMD on clinical outcomes compared to our current standard of care.

MATERIALS AND METHODS

The study was conducted at Karolinska University Hospital in Stockholm, Sweden, from June 1, 2011, to June 30, 2013. Of the 90 consecutive patients who underwent renal transplantation during the enrollment period, 80 chose to participate in the study. Three patients chose not to participate in the study for unclear reasons, 5 were unable to provide consent, and 2 lost their grafts before baseline; the average age of these 10 patients was 50.8 years (standard deviation, 19.2). All participants were enrolled on the transplant surgery ward 7 to 14 days after renal transplantation. The inclusion process and randomization are described below in accordance with Consolidated Standards of Reporting Trials guidelines.[14] The only inclusion criterion was that the patient should understand the informed consent form and agree to participate in the study; the consent of both parents was required for underage patients. The principal investigator informed all participants about the study both verbally and in writing. After giving their verbal and written consents, patients were randomized to intervention or control using prenumbered, sealed, and opaque envelopes in four batches (20 per batch). Each envelope randomly contained a note allocating the patient to either control or intervention. The randomization envelopes were assigned to the enrolled patients in consecutive order (1-80). All patients were followed up for 1 year, and the intervention groups were asked to continue using the EMD for the full year. The patients loaded the EMD with a week's worth of medication at a time. At the prescribed time for taking the medication, the EMD gave visual and audible signals. If the patient did not take their medication, the audible signal was repeated with increasing frequency for 120 minutes. After this (or after the medication was taken), the EMD sent an SMS message to the web-based software, thus providing information about patient compliance. The control group followed standard care.

Six of the 40 participants in the intervention group withdrew from the study prematurely, 3 of them due to "a feeling of being monitored." One participant suffered a stroke and was unable to be responsible for taking medications. One participant died 6 months after inclusion as a result of a serious infection. A few days after the start of the study, 1 participant experienced the EMD to be extremely stressful/worrisome, which resulted in the withdrawal from the study. None of the participants in the control group withdrew from the study prematurely.

TABLE 2.

Flow chart of the study with 10 visits/patients per year

	Visit 1 TX	Visit 2 *random* days 7-14	Visit 3 *week 4* day 28 ±7	Visit 4 *week 8* day 56 ±7	Visit 5 *week 12* day 84 ±7	Visit 6 *week 16* day 112 ±14	Visit 7 *week 20* day 140 ±14	Visit 8 *week 24* day 168 ±14	Visit 9 *week 36* day 252 ±28	Visit 10 *week 52* day 365 ±28
P-creatinine		x	x	x	x	x	x	x	x	x
B-tacrolimus/ B-cyclosporine/ B-sirolimus		x	x	x	x	x	x	x	x	x
P/S MPA/ B-TPMT-metabolites			x		x		x		x	
Web page for EMD[a]		x	x	x	x	x	x	x	x	x
AE/SAE		Continuous								

Follow-up (control group + intervention group).
[a]Applies only to the intervention group.

TABLE 3.

Distribution between intervention group and control group

	Intervention group (n = 40)	Control group (n = 40)	Total X
Living donor	21 pat	15 pat	36 pat
Deceased donor	19 pat	25 pat	44 pat
Sex	15 women/25 men	13 women/27 men	28 women/52 men
Average age, y	44.3 (9-68)	45.0 (2-69)	44.65 (2-69)
Screen failure	1	0	1

No study-specific drugs were administered; all immunosuppressive medications were prescribed according to routine clinic procedure depending on patient-specific needs. All study participants took immunosuppressive medication twice a day; this included tacrolimus in all patients except 1 participant in the intervention group, who was treated with cyclosporine twice daily because of atrial fibrillation. Study participants received tacrolimus either twice daily (Prograf) or in "slow release" form (Advagraf) once daily, because the transplant clinic was also participating in a prospective randomized drug trial (ADVANCE) comparing these 2 preparations in a steroid-free protocol. Immunosuppressive treatment for patients in the 2 groups is summarized in Table 1.

The accepted time interval for taking their medications was from 1 hour before the scheduled medication time until 2 hours after the scheduled time.

Visits, sampling, and time of data collection are presented in Table 2. The data were obtained from patient charts and the web-based software according to the study plan, over 10 visits in 1 year, by 2 of the investigators (J.H., G.T.). Each study visit was registered on an electronic case report form (eCRF) by J.H. Parameters for adherence, renal function (S-creatinine), tacrolimus concentration (B-tacrolimus), information about biopsies, rejection episodes, rejection treatments, and hospital admissions were obtained from the patient chart and entered on the eCRF according to the study plan by J.H. and G.T. Parameters for compliance were obtained from the web-based software (intervention group) and entered on the eCRF according to the study plan by J.H. and G.T. In this study, medication compliance parameters related to the EMD were analyzed, including taking compliance, dosing compliance, variability of dosing intervals, and number of drug holidays. Any medical device-related adverse events or serious adverse events were identified and reported to the EMD manufacturer.

The intervention group used the EMD for a period of 1 year. Drug compliance in the control group was not assessed, because patients in this group did not use the EMD. All data from the eCRF and EMD records were collected in a database for further statistical analysis. Patients were assigned a unique code number, and the analysis was performed in a blinded fashion by the statistician.

Statistical analysis was carried out at the Unit of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. The choice of statistical methods was based on the research questions and the distribution of outcome variables. The number of missed doses over time for the EMD group and the number of readmissions were analyzed using negative binomial regression with random intercepts. Differences in rejection reactions were analyzed using a Poisson regression model with random intercepts. P-creatinine levels and concentrations of immunosuppressive drugs were analyzed by linear regression with random intercepts. In the multivariate analysis, depending on outcome variable, the independent variables were age, sex, intervention, type of immunosuppression, induction therapy, ABO-incompatible transplantation, retransplantation, tacrolimus blood drug concentration, rejection, day of the week, morning/evening dosing, time from transplantation, and missed outpatient clinic appointments. For comparison of background variables between the EMD group and the control group, the 2-sample t test, χ^2 test, or Fisher exact test was used, depending on the distribution of the background variable. For all analyses, P values less than 0.050 were considered to be statistically significant.

Participants were identified by sex and age and assigned a unique study number (01-80).

The results are presented with numerical median value or average value reported in the tables and in the text. Data from participants who were prematurely excluded from the study are presented, but only up to the point of exclusion. The entire study was conducted in accordance with the study protocol, the principles of good clinical practice, and the ethical principles of the Declaration of Helsinki. The Regional Ethical Review Board in Stockholm approved the study on April 28, 2011 (2011/471-31/4). The principal investigator informed the Medical Products Agency medical device division about the study on May 4, 2011.

RESULTS

Demographic background and breakdown of transplants from living or deceased donors are summarized in Table 3. There were no significant differences between groups with respect to sex, age, type of donor, type of immunosuppressant, or previous transplants.

Primary Endpoint

Patients in the intervention group skipped their medicine dose on 524 of 23 820 occasions (2.2%), corresponding to a compliance rate of 97.8%. Of these missed doses, 48% (252/524) occurred in teenagers/young adults aged 16 to 35 years (8/39 study participants). The other age groups missed their doses on equal levels. Women accounted for 60% of missed doses. Missed doses were significantly more common in the evening (308/524; $P < 0.001$). Univariate

TABLE 4.

Compliance over a 12-month period based on the number of missed medicine doses in the intervention group

Compliance with immunosuppressive treatment, mo/%, intervention group							
M1	M2	M3	M4	M5	M6	M7-9	M10-12
11 (99.5%)	27 (98.8%)	46 (97.9%)	67 (96.9%)	33 (98.1%)	37 (98.1%)	124 (96.9%)	179 (96.0%)

The percentages are taken from the web-based software, according to study follow-up visits

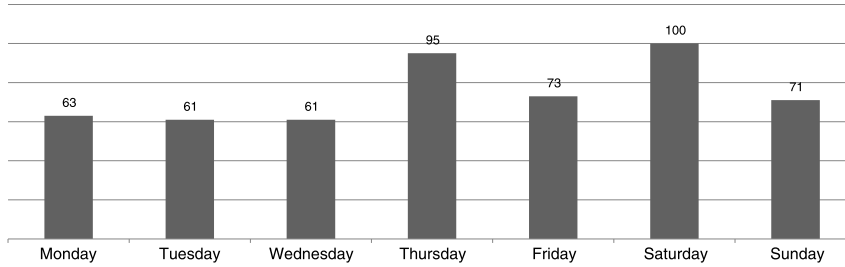

FIGURE 2. Analysis of days of the week of missed doses in intervention group, by number of occasions. Monday, 63; Tuesday, 61; Wednesday, 61; Thursday, 95; Friday, 73; Saturday, 100; Sunday, 71.

analysis showed that patients were 50% more likely to miss the evening dose than the morning dose (incidence rate ratio, 1.50; 95% confidence interval, 1.22-1.85). Missed medicine doses were significantly more common during the second half of the year than during the first half of the year (303/524; P = <0.001; Table 4). Time as a variable with medication discrepancies in univariate analysis showed that the number of missed medicine doses increased by about 20% over time (incidence rate ratio, 1.23; 95% confidence interval, 1.16-1.30). Drug compliance in the control group was not assessed because patients in this group did not use the EMD.

The number of missed doses varied from 1 weekday to the next (P = 0.033), with patients missing their medications most frequently on Thursdays and Saturdays; the distribution of missed medication intake by day of the week is shown in Figure 2. Six participants (15%) from the entire intervention group successfully took their medications at the right time throughout the study.

Of all scheduled outpatient follow-up visits during the 1-year period (22 visits/patient), 6 participants missed a total of 11 visits (1%). Three of these 6 participants had forgotten their appointments 2 or more times. Patients missed outpatient follow-up visits 8 times in the intervention group and 3 times in the control group, including 3 occasions during the first half of the year and 8 occasions during the second half of the year. There was no significant difference between the intervention and control groups.

Secondary Endpoint

The numbers of emergency hospital admissions during the study were followed up for both groups; 22 of 53 admissions were in the intervention group (P = 0.854, n.s.). Reasons for emergency admissions were anemia, ulcers, leg edema, diarrhea, heart attack, ureteral stenosis, lymphocele, hydronephrosis, and rejection therapy.

Rejection

During the study, a total of 92 emergency renal biopsies were carried out among 55 participants, including 32 among 17 participants in the intervention group. Rejection (according to the Banff classification) was diagnosed on 33 occasions, including 6 rejections among 4 participants in the intervention group and 27 rejections among 13 participants in the control group. This difference was significant in a univariate analysis, but did not quite reach significance in a multivariate analysis (P = 0.019 and P = 0.054, respectively). The variables in the multivariate analysis were intervention, Advagraf/Prograf, age, sex, retransplantation, tacrolimus trough levels, standard deviation of tacrolimus trough levels, CellCept/Imurel, induction therapy, ABO incompatibility, and time. Rejections were treated according to routine clinical procedure. The majority of rejection reactions (82%; 27/33) occurred during the first half of the study. One possible rejection during hospitalization after renal transplantation is not reported here, because the nursing staff were responsible for that participant's medication as part of inpatient care.

All rejections (n = 33) were treated with methylprednisolone (500 mg Solu-Medrol/Pfizer) for 3 days. One steroid-resistant rejection in the control group was treated with antithymocyte globulin (Thymoglobulin/Sanofi). The cost of 1 rejection, based on 3 days of hospitalization, radiographic study, pathology analysis, sampling, and the medication Solu-Medrol, was 12 times higher than the cost of 1 year use of an EMD (Swedish Krona (SEK) 90 367 vs SEK 7500). The 6 rejections in the intervention group cost SEK 542 202, whereas the cost of the 27 rejections in the control group was more than 4 times higher at SEK 2 439 909 (Table 5). Four days of treatment with Thymoglobulin cost SEK 35 980 (not included here).

P-creatinine (μmol/L) and concentration of immunosuppressive drugs (tacrolimus, ng/mL) were routinely measured twice weekly over the first 3 months, once a week from then until 6 months, and once a month from 6 months to 1 year after renal transplantation. There was no significant difference in P-creatinine (μmol/L) or tacrolimus concentration between the 2 groups, and rejections did not significantly affect the P-creatinine levels. None of the study participants lost their grafts during the study period.

Immunosuppression

The distribution of the numbers of rejections between Prograf and Advagraf is summarized in Table 6. Of all

TABLE 5.

Breakdown of the costs for rejection, including diagnosis and treatment, for both groups

	Intervention group (EMD)		Control group (no EMD)	
Item	n = 6	Total SEK	n = 27	Total SEK
3 days hospitalization (including ultrasound, biopsy, Solu-Medrol)	68 952	413 712	68 952	1 861 704
Pathology	11 908	71 448	11 908	321 516
Chemistry	4228	25 368	4228	114 156
Immunology	2884	17 304	2884	77 868
Pharmacology	2395	14 370	2395	64 665
Total	90 367	542 202	90 367	2 439 909

TABLE 6.

Rejection after transplantation with prograf or advagraf treatment

No. rejections	Intervention group	Control group	Total
Prograf	4	12	16
Advagraf	0	1	1

participants who experienced rejection episodes, 16 took Prograf and 1 took Advagraf. The difference between Prograf and Advagraf in relation to rejection of the graft was significant in a univariate analysis ($P = 0.026$), but did not reach statistical significance in a multivariate analysis ($P = 0.098$, n.s.).

DISCUSSION

The results of this study show that although compliance in the intervention group was not 100%, it was very high (97.8%). Younger patients (16-35 years) accounted for almost half of the missed medication doses in the intervention group, though they represented only 21% of the study group. Although this difference between younger and older patients did not reach statistical significance, it is in line with the results of other studies as well as clinical experience.[5,8,9,15] The number of missed doses varied significantly depending on the day of the week ($P = 0.033$). Although missed doses on Saturdays are not surprising, participants missed doses on Thursday evenings almost as often, which is difficult to explain. One participating patient suggested that several renal transplant patients do not work a full work week, but are free on Fridays.

The number of missed doses with the EMD increased by about 20% over the study period, indicating that a reminding function for medicine intake may not be sufficient over time. Another study showed that patients with declining medication adherence over time also had more acute rejections.[13] It is possible that a support person (family member, friend, health care staff, and so on) linked to the alarm could help the patient in real time to remember their medicine dose.

Regarding renal function (P-creatinine, μmol/L) and drug concentration (tacrolimus, ng/mL), no significant difference was found between the groups during the first year. It would be of interest to follow the trend between these 2 groups for several years because graft loss due to lack of compliance usually only becomes apparent after several years.[16-18] Multivariate analysis of P-creatinine and the number of skipped doses showed that 3 or more missed doses between study visits were associated with higher levels of P-creatinine (11.69 μmol/L above the mean, n.s.) and lower tacrolimus serum levels (0.71 ng/mL below the mean, n.s.).

One important finding in our study was that the risk of rejection was 3 times lower in the intervention group. This difference was significant in a univariate analysis ($P = 0.02$) but not in a multivariate analysis ($P = 0.054$, n.s.). Because the participants were randomized into 2 groups, the intervention and control groups, univariate analysis is justifiably adequate for this variable. This difference did not correlate with a difference in creatinine levels between the groups. One can speculate that this was due to successful rejection treatment and/or an overly short follow-up.

Regarding immunosuppressive drugs, the experience of the 15 participants in the intervention group who took Advagraf and experienced no graft rejections after transplantation is an interesting finding. Tacrolimus concentrations among patients using Advagraf did not differ markedly between the intervention and control groups (8.1 vs 7.5 ng/mL), but the concentration of tacrolimus did differ between Prograf and Advagraf recipients in both groups (Figure 3). However, the concentrations within the groups were relatively equal.

Other compliance studies[19,20] have shown that the evening dose is more difficult to remember than the morning dose. This was also the case in our study; univariate analysis showed that the patients were 50% more likely to miss the evening dose than the morning dose. We saw no difference in this respect whether patients received Advagraf or Prograf.

The relatively high number of rejections after the first half of the study (82%) and the differences in tacrolimus between

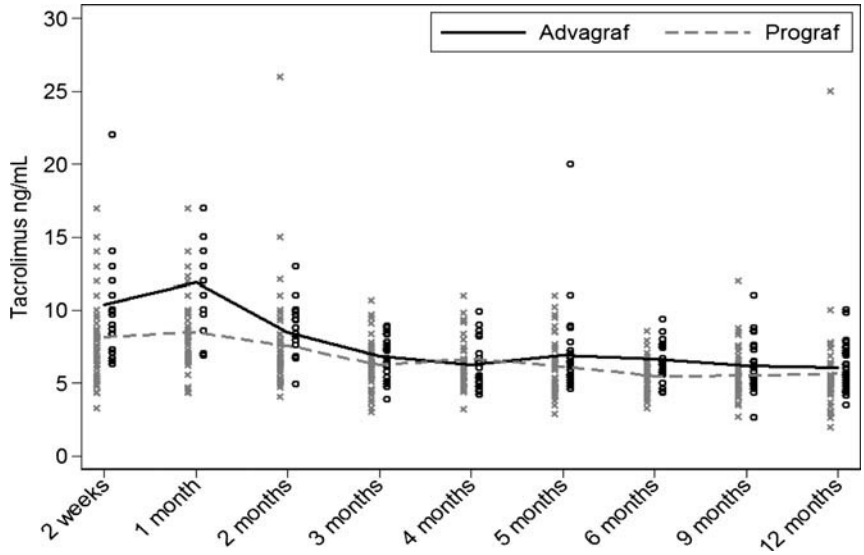

FIGURE 3. Serum concentrations of tacrolimus over time, depending on immunosuppressive treatment with Prograf versus Advagraf (ng/mL).

patients receiving Prograf and Advagraf raise the question of whether the tacrolimus level among the controls was too low.

REFERENCES

1. Pinsky BW, Takemoto SK, Lentine KL, et al. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. *Am J Transplant*. 2009;9:2597–2606.
2. Prendergast MB, Gaston RS. Optimizing medication adherence: an ongoing opportunity to improve outcomes after kidney transplantation. *Clin J Am Soc Nephrol*. 2010;5:1305–1311.
3. Evans RW, Applegate WH, Madsen JC, et al. Cost-related immunosuppressive medication nonadherence among kidney transplant recipients. *Clin J Am Soc Nephrol*. 2010;5:2323–2328.
4. Chisholm MA. Identification of medication-adherence barriers and strategies to increase adherence in recipients of renal transplants. *Manag Care Interface*. 2004;17:44–48.
5. Dobbels F, De Geest S, Decorte A, et al. Adherence to the immunosuppressive regimen in pediatric kidney transplant recipients: a systematic review. *Pediatr Transplant*. 2010;14:603–613.
6. Sabate E (Ed). *Adherence to Long-Term Therapies: Evidence for Action*. Geneva, Switzerland: World Health Organization; 2003.
7. Lennerling A, Forsberg A. Self-reported non-adherence and beliefs about medication in a Swedish kidney transplant population. *Open Nurs J*. 2012;6:41–46.
8. Corteville B, Van Laecke S, Harden P. Non-adherence and clinical outcome of kidney transplantation in recipients aged < 23 years. *Am J Transplant*. 2009;9:516.
9. Dobbels F, Van Damme-Lombaert R, Vanhaecke J. Growing pains: non-adherence with the immunosuppressive regimen in adolescent transplant recipients. *Pediatr Transplant*. 2005;9:381–390.
10. Chisholm-Burns M, Pinsky B, Parker G. Factors related to immunosuppressant medication adherence in renal transplant recipients. *Clin Transplant*. 2012;26:706–713.
11. Sellarés J, de Freitas DG, Mengel M. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant*. 2012;12:388–399.
12. Christensen A, Christrup LL, Fabricius PE. The impact of an electronic monitoring and reminder device on patient compliance with antihypertensive therapy: a randomized controlled trial. *J Hypertens*. 2010;28:194–200.
13. Nevins TE, Robiner WN, Thomas W. Predictive patterns of early medication adherence in renal transplantation. *Transplantation*. 2014;98:878–884.
14. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *J Am Podiatr Med Assoc*. 2001;91:437–42.
15. Rianthavorn P, Ettenger RB. Medication non-adherence in the adolescent renal transplant recipient: a clinician's viewpoint. *Pediatr Transplant*. 2005;9:398–407.
16. Weng FL, Chandwani S, Kurtyka KM. Prevalence and correlates of medication non-adherence among kidney transplant recipients more than 6 months post-transplant: a cross-sectional study. *BMC Nephrol*. 2013;14:261.
17. Folkmane I, Adamsone I, Bicans J. Clinical impact of non-compliance after renal transplantation. *Acta Medica Lituanica*. 2008;15:216–221.
18. Denhaerynck K, Burkhalter F, Schäfer-Keller P. Clinical consequences of non adherence to immunosuppressive medication in kidney transplant patients. *Transpl Int*. 2009;22:441–446.
19. Ichimaru N, Kakuta Y, Abe T. Treatment adherence in renal transplant recipients: a questionnaire survey on immunosuppressants. *Transplant Proc*. 2008;40:1362–1365.
20. Wlodarczyk Z, Squifflet JP, Ostrowski M. Pharmacokinetics for once- versus twice-daily tacrolimus formulations in de novo kidney transplantation: a randomized, open-label trial. *Am J Transplant*. 2009;9:2505–2513.