Intensified pharmaceutical care is improving immunosuppressive medication adherence in kidney transplant recipients during the first post-transplant year: a quasi-experimental study

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ABSTRACT

Background. Medication adherence is critical for transplant patients because the consequences of non-adherence can result in allograft loss and may be life threatening.

Methods. A prospective study with 74 renal transplant recipients using a sequential control group design was performed to investigate the impact of a pharmaceutical intensified care programme led by a clinical pharmacist on daily drug adherence during the first year after renal transplantation. Thirty-nine patients of the control group received the already established standardized drug and transplant training, while 35 patients of the intensified care group (ICG) received additional inpatient and outpatient pharmaceutical care and counselling by a dedicated clinical pharmacist. Applied interventions were clustered and classified using the behaviour change technique taxonomy according to Michie. Adherence to immunosuppressive drug therapy was monitored up to 1 year using a medication event monitoring system, pill count (PC), drug holiday (DH) occurrence, Morisky questionnaire and self-report.

Results. Sixty-seven patients (35 of the standard care and 32 of the ICG) were analysed. Implementation of DA was significantly (P = 0.014) improved in patients of the ICG (91%) compared with SCG (75%) during the first year after transplantation. Daily adherence measures were already improved within 30–40 days after start of intensified patient care and continued throughout the study period. Intensified care patients also showed significantly better results for taking adherence (P = 0.006), PC (P = 0.008) and DHs (P = 0.001).

Conclusions. The additional, intensified pharmaceutical care improved patients’ medication adherence remarkably, suggesting that the applied additional care programme has the potential to improve outcomes after organ transplantation.
**INTRODUCTION**

Medication adherence is critical for immunosuppressive medication in transplant patients because consequences of non-adherence can result in allograft loss or, at worst, loss of life [1-4]. Non-adherence after kidney transplantation is believed to be responsible for ~20% of late acute rejections [5] and up to 36% of graft losses [6, 7]. Recently published results suggest a close relationship between non-adherence and chronic humoral rejections resulting from the development of donor-specific antibodies [8]. Considering the shortage of donor organs and the dramatic consequences of non-adherence, improvement of patient adherence appears essential [6, 7, 9].

Today, medication adherence is defined as ‘the process by which patients take their medications as prescribed, composed of initiation, implementation and discontinuation’ [10]. Initiation (occurs when the patient takes the first dose of the prescribed drug) and discontinuation (occurs when the patient stops to take the prescribed medication, for whatever reason(s)) are inherently discontinuous actions [10]. Therefore, efforts taken to improve implementation (extent to which the patient’s actual dosing corresponds to the prescribed dosing regimen for the time between initiation and the last dose) are most promising for the long-term improvement of patients adherence and clinical outcomes. There have been multiple approaches in the past for a reliable adherence assessment. State of science in adherence measurement is a combination of several methods, including self-report, pill count (PC)/pharmacy refill and electronic measurement [11, 12]. However, the number of studies dealing with possible strategies to enhance medication adherence after kidney transplantation is still very low [13].

Drug adherence is influenced by a variety of factors [5, 14, 15]. Most of these factors such as age, gender, social support or past medical details of the patient are hard to address. Efforts to improve patient-related factors such as patient education, illness perception or medication belief are more promising to influence. This is supported by earlier studies demonstrating that ~75% of the non-adherent population can be positively influenced by educational training or simplified treatment regimens [16, 17]. Therefore, the implementation and evaluation of a multi-factorial intervention approach was tested in this study, using an educational programme [18] carried out in the form of intensified patient counselling by a dedicated clinical pharmacist. The additional pharmaceutical care was adjunct to an already established standardized basic drug and general transplant training programme carried out by doctors and nurses. Overall, it was aimed for an increase of patients’ awareness of the importance of high adherence with their immunosuppressive drug therapy. Our study primarily addressed the implementation component of medication adherence. The aim was to investigate the efficacy of a pharmaceutical care programme comprising and applying a structured adherence management module to enhance kidney transplant patients’ adherence to immunosuppressive medication during the first year after transplantation.

**MATERIALS AND METHODS**

According to the recently published taxonomy for describing and defining adherence to medication [10], this study primarily addressed the implementation element of adherence. It is hypothesized that systematically applied pharmaceutical care comprising counselling and adherence support in addition to standard post-transplant care for 1 year enhances medication adherence. As primary end point, patients’ daily adherence (DA) during the first year post-transplantation was chosen. Secondary outcomes are listed below.

**Study design**

The study was performed as a prospective, controlled, open interventional study using a sequential control group design.

**Study setting and sample**

The study was approved by the Ethics Committee of the Medical Faculty of the University of Erlangen-Nürnberg. Enrollment took place between August 2008 and July 2010. All eligible recipients of a renal transplant at the Erlangen University Hospital (EUH) received verbal and written information about the project within 3–4 days after renal transplantation and were asked whether they would participate in the study. Eligible patients had to be 18 years of age, German-speaking, independent of others for medication management or questionnaire completion and willing as well as able to repetitively visit the outpatient clinic of the Department of Nephrology and Hypertension, for educational training, pharmacy refill and medication event monitoring system (MEMS) data collection. An immunosuppressive regimen including mycophenolic acid [MPA; mycophenolate mofetil (MMF)/MPA] and the usage of the administered MEMS (Aardex Ltd, Sion, Switzerland) bottle for storage of the monitored MMF/MPA therapy during the time of study participation were also mandatory. The study protocol considered a maximum observation period of 365 days after post-transplant hospital discharge.

Study patients who provided written consent were enrolled in either the standard care group (SCG) or the intensified care group (ICG). A sequential study design with repetitive SCG versus ICG enrolment using 6-month episodes was favoured over individual randomization. In the case of individual randomization but less so in the sequential control design, patients of both groups would easily meet and exchange information during their post-transplant recovery on the ward as well as during their following outpatient visits. Figure 1 provides an overview of the study design and illustrates when variables were assessed and the interventions applied.

**Data collection procedures**

On enrolment, patient-related baseline data including age, sex, marital status, degree of education, status of employment, donor type (living or deceased donor), number of transplants (first, second, third or more) and immunosuppressive drug therapy were collected by means of a medical records review. Standard immunosuppressive therapy consisted of induction therapy with basiliximab, calcineurin inhibitor (CNI)
(cyclosporin A/tacrolimus) plus MPA (MMF/MPA) plus steroids either given for 1 year or eliminated by a rapid steroid withdrawal after the first post-transplant week. Patients’ baseline characteristics are summarized in Table 1. Other important patient characteristics/adherence determinants such as health-related quality of life (HRQoL) and patients’ degree of anxiety and depression at hospital discharge were also assessed. Patients in the SCG arm of the study had no additional contact with the clinical pharmacist besides this baseline data collection.

### Adherence measurement

After hospital discharge, adherence monitoring was performed throughout the first year post-transplantation using MEMS. MEMS bottles were provided to every study participant at hospital discharge. Each patient was informed regarding adherence monitoring using MEMS. Drug of choice for the adherence measurement was MPA (MMF/MPA). We chose MMF/MPA for two reasons. First, as part of standard immunosuppression after kidney transplantation, every possible study participant would receive MMF/MPA treatment and therefore every patient would be eligible. Second, MMF/MPA is dosed twice a day very consistently with only a rare number of dose adjustments for each patient (in contrast to CNI medication), which makes adherence measurement by MEMS easily applicable, especially over a long period of time. All patients received their MMF/MPA-containing drugs from the Pharmacy Department during their participation period. Because costs for prescribed drugs in Germany are always covered by either statutory or privately run health insurances, a probable participation bias due to drug cost coverage was not an issue. MEMS data collection and medication refills were performed by the clinical pharmacist during patients’ regular outpatient visits.

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**FIGURE 1:** Design of the study, including when each of the variables were assessed and when each intervention was applied.
uncensored MEMS data are likely to overestimate non-adherence [19], adherence data were censored according to information derived from special documentation sheets that were given to every study participant alongside their MEMS bottles (e.g. exclusion of self-reported non-monitoring intervals, extra bottle openings).

Adherence measurement using MEMS was supplemented by a PC and questionnaire. The PC was assessed during patients’ regularly scheduled refill visits at the outpatient clinic. For the assessment by the questionnaire, we chose a modified version of the Morisky questionnaire [20] consisting of four items and an additional self-report item that has already been used for evaluation of transplant recipients [21, 22]. Validated questionnaires specially designed for transplant populations such as the transplant adherence questionnaire were not available at the time of our study conduct.

Apart from this adherence data collection and the regular MEMS refill, patients of the SCG group had no additional contact with the clinical pharmacist until the end of their study participation.

### Standard care, intensified pharmaceutical care and adherence support

Patients of the SCG received the already established standardized basic drug and general transplant training conducted by doctors and nurses, which took place during the first 2 weeks after transplantation on the hospital ward. The standard training procedure consisted of written information via a 15-page handout explaining post-transplant medication, rejections, infections and tumor risks. A standardized training session of about an hour was conducted once or twice, during which the transplant physician educated the individual patient about the immunosuppressive medication, its dosing, timing, interaction with other medication, meals, or grapefruit juice, and desired effects as well as potential side effects. In an additional, independent training session of ∼1 h, nurses individually trained transplant recipients regarding the practical application of their medication. After discharge, all patients had scheduled follow-up visits at the outpatient clinic of the transplant centre. Here, CNI-blood levels were measured and their dosing adjusted accordingly. Patients also had the opportunity to discuss possible adverse effects of their drug therapy with the doctor in charge.

In addition to this standard transplant training, ICG patients received pharmaceutical care by a dedicated clinical pharmacist. Combining educational, behavioural and technical interventions, the applied pharmaceutical care is a multifactorial intervention approach to enhance patients’ medication adherence. ICG patients had a minimum of three counselling sessions of ∼30 min within the first 2 weeks after transplantation. These counselling sessions were standardized and comprehensively covered all pre-defined aspects of immunosuppressive drug therapy and its importance for the patient/transplant using a checklist. Session one focused on the mechanisms of transplant rejection, immunosuppressive drug actions and dosing as well as a detailed drug–drug interaction check on participant’s complete medication. In session two, patients were counselled on common adverse effects of

### Table 1. Patients’ baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total group</th>
<th>SCG (n = 39)</th>
<th>ICG (n = 35)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [mean (SD)]</td>
<td>53 (12.6)</td>
<td>54 (11.9)</td>
<td>51 (13.3)</td>
<td>0.392</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>69% (51)</td>
<td>62% (24)</td>
<td>77% (27)</td>
<td>0.148</td>
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<tr>
<td>Female</td>
<td>31% (23)</td>
<td>38% (15)</td>
<td>23% (8)</td>
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</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/lives with partner</td>
<td>82% (61)</td>
<td>82% (32)</td>
<td>83% (29)</td>
<td>0.928</td>
</tr>
<tr>
<td>Single</td>
<td>18% (13)</td>
<td>18% (7)</td>
<td>17% (6)</td>
<td></td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>43% (32)</td>
<td>38% (15)</td>
<td>49% (17)</td>
<td>0.381</td>
</tr>
<tr>
<td>Unemployed</td>
<td>57% (42)</td>
<td>62% (24)</td>
<td>51% (18)</td>
<td></td>
</tr>
<tr>
<td>Donor type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living donor</td>
<td>23% (17)</td>
<td>28% (11)</td>
<td>17% (6)</td>
<td>0.259</td>
</tr>
<tr>
<td>Deceased donor</td>
<td>77% (57)</td>
<td>72% (28)</td>
<td>83% (29)</td>
<td></td>
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<tr>
<td>Number of transplants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>91% (67)</td>
<td>90% (35)</td>
<td>91% (32)</td>
<td>1</td>
</tr>
<tr>
<td>Second or more</td>
<td>9% (7)</td>
<td>10% (4)</td>
<td>9% (3)</td>
<td></td>
</tr>
<tr>
<td>Dialysis before transplantation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>99% (73)</td>
<td>100% (39)</td>
<td>97% (34)</td>
<td>0.473</td>
</tr>
<tr>
<td>No</td>
<td>1% (1)</td>
<td>0</td>
<td>3% (1)</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressive drug therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>82% (61)</td>
<td>82% (32)</td>
<td>83% (29)</td>
<td>0.928</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>18% (13)</td>
<td>18% (7)</td>
<td>17% (6)</td>
<td>0.956</td>
</tr>
<tr>
<td>Mycophenolic acid—sodium</td>
<td>20% (15)</td>
<td>21% (8)</td>
<td>20% (7)</td>
<td></td>
</tr>
<tr>
<td>Mycophenolic acid—mofetil</td>
<td>80% (59)</td>
<td>79% (31)</td>
<td>80% (28)</td>
<td></td>
</tr>
<tr>
<td>Steroid withdrawal within the first 8 days</td>
<td>20% (15)</td>
<td>18% (7)</td>
<td>23% (8)</td>
<td>0.600</td>
</tr>
<tr>
<td>Antibody induction therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basiliximab</td>
<td>82% (61)</td>
<td>82% (32)</td>
<td>83% (29)</td>
<td>0.641</td>
</tr>
<tr>
<td>Anti-thymocyte globulin</td>
<td>16% (12)</td>
<td>18% (7)</td>
<td>14% (5)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2% (1)</td>
<td>0</td>
<td>3% (1)</td>
<td></td>
</tr>
</tbody>
</table>
their immunosuppressive drugs as well as prophylaxis, detection and possible self-treatment of these effects. Possible interactions between immunosuppressive drugs and food were also addressed. Key messages of both sessions one and two were backed up by written information material. Session three exclusively dealt with adherence support, including identification of possible reasons for non-adherence, defining feasible adherence-enhancing strategies as well as prophylaxis (cue dosing, cell phone reminders) [23, 24] of unintentional non-adherence. After discharge, pharmaceutical care continued, utilizing primarily the contents of inpatient counselling session three, but when necessary also of the first sessions. In contrast to SCG education, ICG patient training was strictly individualized, repetitive and redundant, covered 12 months instead of 2 weeks, included more aspects and provided practical hints and strategies for medication management. Counselling sessions took place at least once quarterly up to a maximum of once monthly during the patient’s follow-up visits at the outpatient clinic of the transplant centre. Patients were also encouraged to contact the pharmacist in case of further questions at any time via phone or email.

A summary and classification of our intervention according to the newest version of intervention taxonomy published by Michie et al. [25] is provided in Table 2. The effect of the additional counselling was measured as difference in patients’ daily medication adherence after the first year of transplantation using MEMS.

**Measured outcome parameters**

The primary objective of this study was to investigate if and to what extent further pharmaceutical care could improve patients’ adherence with their MMF/MPA therapy during the first year after transplantation. The primary outcome parameter was patients’ DA (percentage of days with the correct dosing of MMF/MPA). Grouping the collected adherence data from a 1-year monitoring period into a single percentage leads to a loss of information regarding the variability of adherence and its evolution over time. In order to get a better view on patients’ implementation of the prescribed MMF/MPA dosing regimen, we executed a longitudinal analysis of the collected DA data [26], using all data points available.

Secondary outcome parameters were taking adherence (TA, percentage of doses taken (bottle opening) in comparison to the total number of doses prescribed), timing adherence (TiA, percentage of doses taken within a 6-h interval [±3 h] around patients standard intake time), adherence rates measured by PC and number of drug holidays (DHs, no MMF/MPA intake for >48 h). Patients’ adherence was also monitored using the Morisky questionnaire including a self-report form (Table 3). Patients were classified as being adherent or non-adherent for every single measurement parameter by the criteria defined in Table 4.

Transplant function was calculated by estimated glomerular filtration rate (eGFR; modification of diet in renal disease IV formula), and the number of biopsy-proven rejections was also assessed. Changes in HRQoL were assessed using the short form 36 (SF-36) questionnaire, consisting of 36 questions examining the patient’s experienced degree of HRQoL, summing the answers in two subscales [physical subscale (PhysSuSca) and mental subscale (MenSuSca)] [27–29]. The degree of anxiety and depression at hospital discharge was investigated using the Hospital Anxiety and Depression Scale (HADS)-D questionnaire [30–32], which is a 14-item questionnaire examining the patient’s degree of anxiety (seven questions) and depression (seven questions) at hospital discharge. The maximum score for both scales is 21 points, classifying a result <7 as unremarkable, scores between 7 and 13 as borderline and scores ≥14 as remarkable with a recommendation for therapeutic intervention. Both questionnaires have already been used on transplant populations in the past [27, 33–35].

**Statistics**

Sample size calculation was done in co-operation with WiSP (Wissenschaftlicher Service Pharma GmbH, Langenfeld, Germany). The mean DA (as the primary objective) was expected to be 80% [standard deviation (SD) ±10%]. An improvement in DA of 10% within the ICG was considered to be clinically relevant. To prove significance for such an improvement, sample size calculation for the primary end point showed that a minimum of 58 analysable patients (29 patients per group) at study end would be needed [α = 0.025 (one sided), (1 − β) = 0.80]. With an estimated drop-out rate of 10%, the
inclusion of at least 64 patients was planned. Final analysis was performed as modified intention-to-treat (ITT) analysis. Per protocol pre-specification, patients who fell below a limit of 30 days of adherence monitoring period were excluded from the final statistical analysis since their information value was too low compared with the observation period of 365 days. Descriptive statistics are given using mean and SD together with their 95% confidence limits or median and percentile range if more appropriate. Comparison and analysis of continuous and discrete variables were performed using \( t \)-test or Mann–Whitney \( U \)-test. Analysis and comparison of categorical variables were executed using \( \chi^2 \)-test or Fisher’s exact test. Testing for statistical significance was always carried out using two-tailed tests. Longitudinal data analyses were conducted by a generalized linear mixed model. The threshold value for statistical significance was 5%. All statistical analyses were conducted using IBM SPSS 21.0 full version for Windows and the statistical package R (version 2.15.3, http://www.r-project.org/).

RESULTS

A total of 184 renal transplant recipients were assessed for eligibility: 70% (129 patients) met the inclusion criteria and were informed about the project. Fifty-seven per cent of those patients (74 patients) submitted their written consent to participate. Ten per cent of the 74 (7 patients) were secondarily excluded from the study and the modified ITT analysis via the pre-specified exclusion criterion: using an MEMS device for <30 days after hospital discharge; the remaining 90% (67 patients) were included in the final statistical analysis. A patient flowchart and reasons for drop-out as well as reasons for not being included and being classified as not eligible are shown in Figure 2. Main reasons for not participating in this study were severe language problems, daily dependence on others help, denial of studies as well as organizational reasons (outpatient care at the second clinic site, long distance travelling). Baseline characteristics of all patients included into the study are demonstrated in Table 1.

Primary outcome parameter

Patients’ implementation of the prescribed dosing regimen was analysed by evaluating the day-by-day percentage of transplant recipients with correct dosing over the study period. Implementation of DA was significantly \((P = 0.014)\) improved in patients of the ICG \([91\%, \text{ confidence interval (CI) 90.52–91.94}]\) compared with SCG \([75\%, \text{ CI 74.57–76.09}]\) during the first year after transplantation (Figure 3). Clear discrimination of the two graphs representing DA of the ICG or SCG could already be seen at Day 30–40 after transplantation.

Secondary outcome parameters

ICG patients also showed better results for TA and PC (Figure 4A and C) as well as for the number of DHs. The mean TA (SD) was 82% (20.2) for the SCG and 95% (7.15) for the ICG \((P = 0.006)\). As seen in Figure 4A, TA rates ranged from 24 to 101% (CI 75.32–88.40) in the SCG and from 70 to 103% (CI 90.52–91.94) in the ICG.
Correct dosing is defined when the number of medication intakes that occurred that day is as prescribed. The mean DA for ICG (upper horizontal line (91%)) was significantly better compared with SCG (lower horizontal line (75%)) (P = 0.014).

92.44–97.34) in the ICG. The mean PC adherence rates (SD) were 90% (11.99) for SCG and 97% (7.33) for ICG patients (P = 0.008) as indicated in Figure 4B. The mean TiA (SD) was 94% (7.33) for SCG and 95% (7.88) for ICG patients. Results ranged from 58 to 104% (SCG) and 76 to 109% (ICG), respectively.

In contrast, results of TiA measurement showed no significant differences, albeit a slight numerical improvement for the ICG patients (P = 0.142, Figure 4B). The mean TiA (SD) was 94% (7.33) for SCG and 95% (7.88) for ICG patients. Results ranged from 75 to 100% within the SCG (CI 91.22–95.97) and from 61 to 100% within the ICG (CI 92.38–97.79).

The results of adherence measurement using the Morisky questionnaire are shown in Table 3 and demonstrate no differences between the two groups (P-values: 0.992 (baseline), 0.526 (6 months after discharge) and 0.524 (study end)). Analysis of the self-report form showed results similar to those of the Morisky questionnaire. At baseline, eight patients from each of the two groups admitted at least one missed drug intake in the past 2 weeks (SCG 8 of 39 patients and ICG 8 of 35 patients; P = 0.807). Six months after transplantation, no patient within the SCG but three patients within the ICG stated a missed drug intake within the past 2 weeks (0 of 35 SCG patients and 3 of 30 ICG patients; P = 0.055). At study end, the number of patients with at least one missed drug intake had increased from zero to one within SCG and from three to four in the ICG (P = 0.193).

After analysing the collected adherence data for each patient, patient classification as adherent or non-adherent was carried out using the seven single adherence parameters (using the terms defined in Table 4). The number and percentage of adherent transplant recipients in the SCG versus ICG are shown in Table 4 and demonstrate significant differences for the number of patients being adherent in multiple parameters such as DA (P = 0.015), TA (P = 0.015) or DHs (P = 0.001). Hereby, patients had to be dichotomized in ‘no drug holidays during study period’ and ‘one or more drug holidays during study period’. Within the SCG, only 15 of 35 patients (43%) did not take a DH during the observation period, in contrast to 26 of 32 patients (81%) within the ICG (P = 0.001).

Only three patients experienced biopsy-proven transplant rejections within their first year after transplantation. Two patients were part of the SCG and one of the ICG group. Rates for the occurrence of rejections in both groups were not different (P = 0.54). Interestingly, all three patients showed DA rates <80% and had at least one recorded DH during observation.

Transplant function improved in both groups over time but was similar at study end [mean glomerular filtration rate in SCG: 46 mL/min (SD: 15.4) versus 49 mL/min (SD: 14.3) in ICG, P = 0.446]. The confidence limits for SCG and ICG are (41.02–50.99) and (43.9–53.68), respectively.

HRQoL or HADS parameters were not influenced as a result of additional pharmaceutical care. P-values for the physical sum scale (PhysSuSca) and mental sum scale (MenSuSca) of the SF-36 questionnaire at the different points of estimation were 0.330 (PhysSuSca) and 0.178 (MenSuSca) at baseline, 0.179 (PhysSuSca) and 0.244 (MenSuSca) at 6 months after transplantation and 0.329 (PhysSuSca) and 0.419 (MenSuSca) at study end. Mean scores (SD) for the anxiety scale were 4.33 (2.95) for SCG and 4.74 (3.48) for ICG patients (P = 0.266). Mean scores for the depression scale were 2.64 (2.80) for the SCG and 2.89 (3.36) for the ICG (P = 0.193).

Our data set was reanalysed using propensity score matching (nearest-neighbour procedure) to verify the homogeneity of the study groups. Hereby, we found 32 well-matched neighbour pairs excluding only three data sets of participants indicating well-balanced raw data. The propensity score matching with these 32 pairs confirmed all results (data not shown).

In addition, differences between both groups regarding DA, TA or PC remained robust and still significant, even when the classification criteria for adherence/non-adherence as shown in Table 4 were changed to 85% (data not shown).

**DISCUSSION**

The main finding of this study is that immunosuppressive medication adherence of kidney transplant patients can be markedly improved through an intensified educational patient care programme comprising specific adherence support carried out by a clinical pharmacist in addition to a standard care programme, which already includes elements of patient education.

This study is novel, in that no comparable study of similar size has yet been conducted combining MEMS measurement, patient counselling by a clinical pharmacist and specific medication adherence support in kidney transplant recipients. As assessed by electronically compiled data using MEMS, daily drug adherence, TA and the frequency of DHs were improved by...
the applied intensified pharmaceutical patient care programme. This result is robust because significant improvement via the intensified care programme was confirmed after either propensity score matching or changing the definition limits of adherence/non-adherence to >85%/<85% or considering the results of the PCs. The extent of DA improvement in the SCG (75%) to the ICG (91%) by >15% is striking and even superior to the conversion of a twice-daily to a once-daily immunosuppressive drug such as demonstrated in a recent study using two different tacrolimus formulations, where DA was improved from 78.8%...
(twice daily) to 88.8% (once daily) [26]. Implementation of our twice-daily immunosuppressant regimen started to be clearly better in the ICG compared with the SCG ~30–40 days after renal transplantation and start of the intervention. Considering that all SCG study patients received their standard education during the first 2–3 weeks, the robust effect of adherence improvement via the intensified training programme could be achieved quite rapidly and continued throughout the study period of 1 year.

We consider a year-long measurement of adherence using MEMS a specific strength of our study. One of the main limitations of the use of MEMS is that bottle opening does not necessarily reflect drug intake. Several assumptions [equipment functioned correctly, bottle opening corresponds with actual drug intake, electronic monitoring (EM) did not influence patients daily life] need to be fulfilled for internal and external validity of MEMS data [19]. During this study, no problems considering equipment malfunction occurred and a special documentation sheet given to patients at discharge was used. The positive influence of using the MEMS on patients’ daily life and adherence [19, 36] as well as being a study participant in general was reduced by the length of the study. While these factors became ‘routine’ for the participants, the pro-adherent effect of the intensified care programme could be demonstrated throughout the whole observation period. Numerous previous studies examining different groups of patients, including patients with infectious diseases [37–39], organ transplant recipients [22, 40], patients with diabetes [41] or high blood pressure [42, 43] have shown that the data collected with MEMS are in fact very reliable [44]. Dobbels and de Geest [11] requested a combination of different measurement methods to get best insights into patients’ adherence. There- fore, adherence measurements via MEMS in this study were complemented by several questionnaires as well as pill counting, thus allowing a comparison of different methods and confirmation of the MEMS-related data.

While some progress was made by implementing new immunosuppressive drugs into routine care during the last two decades, modern treatment strategies such as CNI freedom or minimization did not produce consistently convincing results and are still controversially discussed [45–47]. Recent studies in renal transplant recipients with worsening renal function demonstrated that allograft loss was most frequently associated and predicted by signs of either humoral or cellular rejection and not by nephrotoxicity [8, 46]. Hereby, non-adherence was more frequent in patients who progressed to renal failure (32%) compared with those whose kidney transplants continued to work (3%) [8]. These and other studies suggest that inadequately or insufficiently low immunosuppressive therapy, regardless of the underlying cause, is a central problem for the long-term survival of the allograft and non-adherence may be a relevant contributing factor.

Overcoming medication non-adherence in solid organ transplant populations could, therefore, be a major pathway for improving clinical outcomes [36]. There were no significant changes in clinical relevant end points measureable in this study, but the study was neither designed nor sufficiently powered to assess an impact on clinically relevant end points such as acute rejections, graft loss or renal function. However, several studies in the past have already demonstrated the influence of patients’ adherence on long-term outcome [4, 48, 49]. In combination with the marked pro-adherent effect of our intensified pharmaceutical care programme, the results of these studies suggest that the implementation of a intensified educational programme in routine clinical care could be of substantial clinical relevance for long-term allograft survival. Rejection rates were low in both arms of this study, which is likely due to the use of quadruple immunosuppressive drug therapy. While the sample size was too low to show significant changes in clinical end points, it is interesting that all rejecting transplant recipients had a DA of <80% and one or more DHs.

This study has several limitations: while it was accurately powered for assessing the primary outcome parameter, it was not powered to test for effects on graft outcome—for which a much larger prospective trial would be needed. Although we intentionally chose a sequential enrolment of patients to facilitate a better separation of our training groups compared with strict randomization, personal interaction between the two study groups cannot be completely excluded. In addition, a selection bias is possible, because only 40% of all transplanted patients participated in the study. Knowing that non-participants tend to be poorer adherers, the generalizability of our results can be challenged. Considering the different reasons for non-participation, a fraction of the 43 patients denied to participate in studies in general or in this MEMS study specifically. The other 74 non-participating patients were excluded almost exclusively due to organizational reasons (38 patients), and language barrier (36 patients), reasons that would have interfered with the conduct of the study in both arms. Therefore, we think that the results of our study are applicable for any adult transplant patient who is in principle willing to participate in studies and has no severe language barrier or is largely dependent on the help of someone else. Furthermore, adherence measurement, follow-up and the educational programme

### Table 4. Number of patients classified as adherent for the seven measured adherence parameters

<table>
<thead>
<tr>
<th>Adherence parameter</th>
<th>Limits for being classified as adherent</th>
<th>SCG (n = 35)</th>
<th>ICG (n = 32)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA</td>
<td>≥80%</td>
<td>57% (20)</td>
<td>84% (27)</td>
<td>0.015</td>
</tr>
<tr>
<td>TA</td>
<td>≥90 and ≤110%</td>
<td>57% (20)</td>
<td>84% (27)</td>
<td>0.015</td>
</tr>
<tr>
<td>TIA</td>
<td>≥80%</td>
<td>86% (30)</td>
<td>97% (31)</td>
<td>0.110</td>
</tr>
<tr>
<td>PC</td>
<td>≥90 and ≤110%</td>
<td>63% (22)</td>
<td>84% (27)</td>
<td>0.047</td>
</tr>
<tr>
<td>DHs</td>
<td>No DHs recorded</td>
<td>43% (15)</td>
<td>81% (26)</td>
<td>0.001</td>
</tr>
<tr>
<td>Morisky questionnaire (12 months)</td>
<td>Answering all four questions with ‘no’ (fully adherent)</td>
<td>63% (22)</td>
<td>63% (20)</td>
<td>0.695</td>
</tr>
<tr>
<td>Self-report (12 months)</td>
<td>No missed intake during the last 2 weeks</td>
<td>77% (27)</td>
<td>72% (23)</td>
<td>0.193</td>
</tr>
</tbody>
</table>

*For Morisky analysis, patients being medium adherent and non-adherent were summarized as non-adherent.*
were limited to 1-year post-transplantation. Whether this intervention during a 1-year period would need to be continued with the same intensity during subsequent years to ensure sustained improvement in adherence is likely but remains unclear. The relatively high level of non-adherence within the SCG is striking but in line with other studies, where patients’ DA for tacrolimus was found to be 78% [26]. Similar results were published in 2009 for a German sample of liver transplant patients [22]. It is likely to assume that well-known contributors to the reliability of MEMS-collected data (e.g. bottle handling) had an effect. As explained earlier on, this was taken into account while designing this study and measures were taken to avoid these contributors having a substantial influence on the collected data (patient information on EM and written information on MEMS handling).

It is unquestionable that adherence levels close to a 100% are desirable, but the discussion about limits of clinical meaningful non-adherence is still ongoing. While recent literature demands adherence levels of up to 95% [11, 50], it remains the major question, how this can be achieved with justifiable effort. In this context, our result of 91% DA in the ICG is remarkably close to these goals of adherence implementation. It remains to be determined whether the combination of simplified once-daily drug regimens with DA rates of >88% [26] can be further improved with an intensified educational care programme up to adherence values beyond 95%.

In conclusion, this study demonstrates that an additional intensified post-transplant pharmaceutical care programme is an effective intervention to substantially improve patients’ adherence regarding immunosuppressive medication within the first year after kidney transplantation. Pharmaceutical care was easily integrated into routine patient care and appears to be universally applicable for any transplant programme. Considering the overall importance of medication adherence for long-term allograft outcome, the study results therefore suggest that pharmaceutical counselling has the potential to improve graft function, which should be further explored in large-scale, multi-centre studies.

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CONFLICT OF INTEREST STATEMENT

None declared.

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