ORIGINAL ARTICLE

Evaluation of tools for annual capture of adherence to immunosuppressive medications after renal transplantation – a single-centre open prospective trial

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SUMMARY

Annual assessment of adherence would strengthen long-term outcome assessments from registry data. The objective of this study was to evaluate tools suitable for annual routine capture of adherence data in renal transplant recipients. A single-centre open prospective trial included 295 renal transplant recipients on tacrolimus. Two-thirds of the patients were included 4 weeks post-transplant, randomized 1:1 to intensive or single-point adherence assessment in the early phase and 1-year post-transplant. One-third were included 1-year post-transplant during a cross-sectional investigation. Adherence was assessed using multiple methods: The "Basel Assessment of Adherence to Immunosuppressive Medication Scale" (BAASIS©) questionnaire was used to assess self-reported adherence. The treating clinician scored patient's adherence and tacrolimus trough-concentration variability was calculated. In the analyses, the data from the different tools were dichotomized (adherent/nonadherent). The BAASIS© overall response rate was over 80%. Intensive BAASIS© assessment early after transplantation increased the chance of capturing a nonadherence event, but did not influence the 1-year adherence prevalence. The adherence tools generally captured different populations. Combining the tools, the nonadherence prevalence at 1 year was 38%. The different tools identified to a large degree different patients as nonadherent. Combining these tools is feasible for annual capture of adherence status.

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Key words
adherence, Basel Assessment of Adherence to Immunosuppressive Medication Scale, clinician's score, tacrolimus variability

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Introduction

After kidney transplantation, patients are in need of life-long immunosuppressive (IS) therapy in order to avoid acute rejection (AR) episodes. The cornerstone in modern immunosuppression is the calcineurin inhibitor tacrolimus (Tac), usually combined with mycophenolate mofetil (MMF) and prednisolone [1,2]. Tac has a narrow therapeutic window and shows significant pharmacokinetic variability [3]. Intensive therapeutic drug

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monitoring (TDM) is mandatory, and high intraindividual variability of Tac-concentrations has been identified as a risk factor for AR and graft loss (GL) [4–8]. Nonadherence can contribute to Tac variability (TacVar), and is associated with AR, decreased graft survival, GL [9–11] and increased costs [12]. Everyday optimal adherence to the IS treatment is a challenge for renal transplant recipients (RTxR) [13]. The European Society for Patient Adherence, Compliance and Persistence defines medication adherence as "the process by which the patients take their medications as prescribed" [14]. Nonadherence can occur in three different phases: initiation (patient do not initiate treatment), implementation (actual dosing does not correspond to the prescribed dosing regimen because of delays, omits or extra doses) or persistence (discontinuation of treatment) [14,15]. Several available tools are used to capture medication adherence in RTxR [16]. There is no gold-standard [17], but electronic monitoring devices are often considered most reliable [18]. However, the data collection is often complex, and hence not applicable for use in quality registries [19]. For large-scale adherence assessments, sparse sampling methods like self-report, healthcare professional assessments and biochemical measures are commonly used, preferably in combination [20,21]. Currently, the "Basel Assessment of Adherence to Immunosuppressive Medication Scale" (BAASIS©) is frequently used in transplantation [22], capturing both if every dose is taken and at the prescribed time [23].

Identification of potential risk factors is important when trying to improve long-term outcomes in RTxR. In Norway, all RTxR are included in a national quality register (The Norwegian Renal Registry), which collects annually data. Including IS adherence in the registry would strengthen analyses of central outcome measures, that is, patient- and graft survival [24–27]. The primary objective of this study was to evaluate tools suitable for annual capture of IS adherence in the quality register.

Materials and methods

Study design and population

The study was performed at the national transplant centre in Norway (Oslo University Hospital – Rikshospitalet) and embraced both a prospective, randomized, open study design in one patient cohort (Group A) and a cross-sectional investigation in another cohort (Group B) as outlined in Fig. 1. RTxR on Tac-based immunosuppression, understanding Norwegian or English, and who managed their IS medications themselves, were eligible for inclusion.

Adherence assessment may in itself potentially affect a patient′s adherence [15]. To control for the increased awareness of adherence behaviour, the study consisted of two groups: Group A was included in the early post-transplant phase and followed for 1 year, while Group B was included when returning for a 1-year preschedule control. To quantify how often adherence should be assessed, or if more frequent assessment actually picks up more events, Group A was in addition randomized to an intensive follow-up Group (A1) or a single assessment Group (A2).

Group A

Two hundred consecutive RTxR were to be included 4 weeks post-transplant, and randomized 1:1 to either an intensive follow-up Group (A1) or a single assessment Group (A2; Fig. 1). The allocation sequence was generated using the "blockrand"-function in R with variable block sizes [28]. Preprepared numbered envelopes containing treatment group were allocated consecutively at inclusion. In A1, the self-reported adherence assessment was performed fortnightly between 4 and 14 weeks post-transplant, as well as 2- and 4 weeks after the 1-year investigation. A2-patients only performed self-reported adherence assessment at 8 weeks and 1-year post-transplant. In addition, tablet counting was performed in A1-patients.

Group B

One hundred previously RTxR returning to the transplant centre for the 1-year routine investigation, were consecutively included and evaluated for adherence at that visit as well as after 2- and 4 weeks.

The trial was performed in accordance with the Declaration of Helsinki and the local ethics committee approved the study (Number 2014/865). All patients gave written informed consent.

Immunosuppressive treatment

All patients received IS induction depending on immunological risk (basiliximab, thymoglobulin or rituximab). Maintenance therapy consisted of Tac in combination with MMF and steroids. The starting dose of Tac was 0.04 mg/kg twice daily for standard-risk patients and 0.05 mg/kg twice daily for high-risk

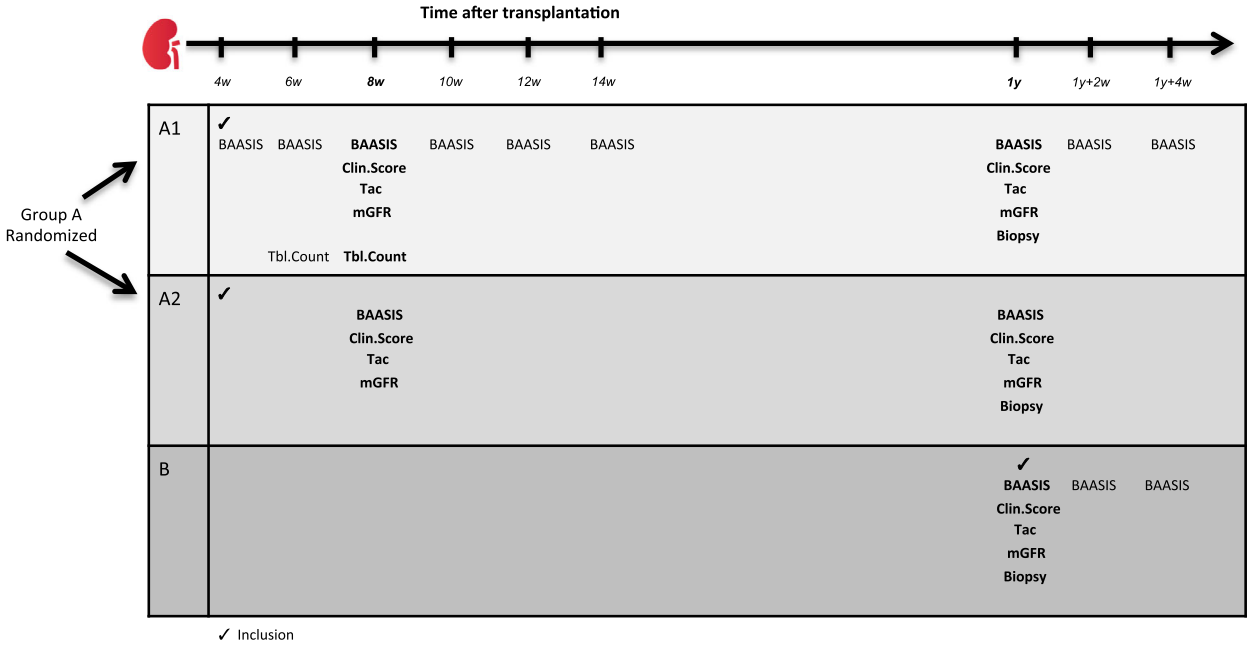

Figure 1 Timeline of study procedure. The schedule of the used adherence tools in the different groups is shown. Clin.Score, clinician's score; mGFR, measured glomerular filtration rate; Tac, tacrolimus trough blood concentrations; Tbl.Count, tablet count; Tx, transplantation; w, weeks; y, years.

patients. Tac doses were individualized to a trough-concentration range of 3–7 μg/l in standard-risk patients, and initial 8–12 μg/l the first 8 weeks followed by 6–10 μg/l in high-risk patient. In the early phase, all received twice-daily Tac formulation (Prograf®) and blood trough-concentration was measured up to four times per week. With time, monitoring frequency was reduced to once a week. After 8–10 weeks, patients left the transplant centre and were followed by their local nephrologist. Switch to once-daily Tac formulation (Advagraf®), after 8 weeks was a joint decision between the patients and the treating physician. The physician was not informed about what group the patient had been randomized into (A1 or A2). MMF was started at 750 mg twice daily and later adjusted according to side-effects, while steroids were administered according to fixed tapering schedule; initially 20 mg/day, tapered to a maintenance dose of 5 mg/day by week 8.

As part of standard of care, all patients implemented the IS medications with support from healthcare personnel with one-to-one education the first weeks post-transplant. Necessary medications were provided free of charge by the public health system. All IS doses were registered in a patient drug diary the first 8 weeks post-transplant, and in case of IS dose changes, written and/or oral information from the treating physician was given to the patient.

Adherence tools

The results from the different adherence tools were dichotomized (Table 1 for definitions). The phases of medication adherence studied were implementation and persistence.

BAASIS©

BAASIS© written questionnaire has been validated in RTxR [29], and was used to assess self-reported adherence to IS medication. Based on the English version, the questionnaire was translated into Norwegian according to guidelines [30]. BAASIS© captures adherence from the last 4 weeks, and consists of five questions on both implementation and persistence: missed a dose, drug holiday (skipped two or more doses), time deviation (>±2 h), dose changes or discontinuation of the IS medications without consulting the physician. Nonadherence was defined as "yes" to any of the questions. In addition to the overall interpretation of BAASIS© as adherent (Ad) or nonadherent (NoAd), the answers were divided into subclasses called *medication taking* nonadherence for the taking dimension, and *medication timing* nonadherence for the timing dimension. The form was primarily answered online (link sent via e-mail) and encrypted data stored directly at the University of Oslo services for sensitive data (TSD 2.0).

Table 1. Definition of nonadherence by different adherence tools.

Tool	Definition of nonadherence
BAASIS©	Missed one or more doses and/or a time deviation >2 h from prescribed time the last 4 weeks
Timing dimension	Took all prescribed doses, but had a time deviation >2 h from prescribed time the last 4 weeks
Taking dimension	Missed one or more doses the last 4 weeks
Clinician's score	Physician/nurse scored patients adherence as suboptimal or poor (≠ excellent)
Tac variability	A CV% >30 (at 8 weeks using six and at 1 year three Tac-concentrations)
Tablet count	A counting that corresponded to <90% or >110% of prescribed dosing schedule during a 2-week period

CV, coefficient of variation; h, hours; Tac, tacrolimus.

Patients not conversant with Internet were allowed to use paper forms. The coherence between the online form and the paper form was checked in a pilot study. The completion time for the form was less than 5 min. Patients not delivering their forms were reminded once after 3–7 days.

Clinician's score

The treating physician/nurse that followed the patient closely in the early post-transplant phase (Group A), as well as the local nephrologist at the 1-year investigation (Group A and B), scored patients individual adherence on a 3-point scale: "poor", "suboptimal" or "excellent" [20]. "Excellent" was interpreted as Ad, "poor" and "suboptimal" as NoAd.

Tac variability

A total of six Tac-concentrations were obtained from the standard TDM data in the early post-transplant phase (6–9 weeks after transplantation), all from outpatients. For the 1-year assessment, at least three Tac-concentrations during the last 3 months were obtained. The coefficient of variation (CV) of Tac-concentrations was calculated as:

$$CV\% = (\sigma/\mu) \times 100,$$

where σ is the standard deviation and μ the mean Tac-concentration. A CV% >30 was interpreted as NoAd [4,8,31]. In the early post-transplant phase, rich data were available for TacVar calculations. In conjunction to the 1-year investigation, Tac measurements were more spaced in time. Blood samples for Tac measurements were drawn immediately before the morning dose. In the early post-transplant phase, all blood levels were measured at the transplant centre, using chemiluminescent microparticle immunoassay (CMIA, analysed on the Architect Instrument; Abbott Laboratories, Abbot Park, IL, USA) until August 2015, then liquid chromatography-tandem mass spectrometry assay (LC-MS/MS) was used. For CMIA, the lower limit of quantification (LOQ) was 1.0 μg/l and the imprecision CV 9% at 2.3 μg/l and 6% at 7 μg/l. For LC-MS/MS, LOQ was 1.1 μg/l and imprecision CV 5.2%. During the 1-year follow-up time, the concentrations were measured using either CMIA or LC-MS/MS. For each individual patient, all Tac-concentrations were measured with the same method.

Tablet count

In the early post-transplant phase, a tablet count of Tac, MMF and steroids was performed in Group A1. A tablet count was performed between two clinical visits, separated by 2 weeks. A count within 90–110% of the individual dosing schedule was defined as Ad [32,33]. In clinical practice, this means a patient could have missed two doses of the twice-daily formulations (Tac, MMF) and/or one dose of the once-daily formulation (steroids) during that period.

Clinical outcome

Four-weeks to 1-year biopsy-proven AR (BPAR) rates, GL and overall mortality were obtained from patient charts for all included patients. At the 1-year investigation at the transplant centre, both *de novo* donor-specific antibodies (dnDSA) and measured glomerular filtration rate (mGFR, 2-point iohexol plasma clearance) were assessed.

Statistical analysis

Data were checked for normality by visual inspection of histogram, Q-Q Plot and box-plot and with the

Shapiro–Wilk test. Skewed variables were log-transformed before parametric statistical analyses were performed. For group comparison, independent sample *T*-test was used for continuous variables and Pearson's chi-square or Fisher exact test for categorical variables. Adherence data obtained from the different tools were all analysed as a dichotomous variable. The main analysis included BAASIS© scores at 8 weeks and 1 year. If a patient had not answered BAASIS© at 8 weeks or 1 year, answer closest in time within respective assessment period was used. For comparison of outcome variables in Ad and NoAd patients, independent sample *T*-test was used. Adherence changes over time in the same patients were calculated using McNemar's test. The agreements between the different adherence tools were analysed using Cohen's kappa, and crosstabs were used to investigate overlap. Univariate logistic regression was used to calculate odds ratios (OR) for nonadherence. To assess if adherence was a predictor for the development of dnDSA or BPAR, a Cox regression analysis using the coxphf package in R was performed [28,34]. A two-sided *P*-value <0.05 was considered significant.

Results

Patients

Of 403 patients transplanted from October 2014 through May 2016, a total of 237 were available for inclusion (Group A): 37 did not meet the inclusion criteria (11 not on Tac, 15 not managed their own medications, 11 did not understand Norwegian/English), 45 patients were still hospitalized 4 weeks after transplantations and not available for inclusion, five experienced graft loss or death in the early post-transplant phase, and 79 were not considered for inclusion as the research laboratory was closed during holidays. Of these 237 patients, 34 (14%) refused participation resulting in inclusion and randomization of 203 patients (Fig. 2). Four included patients (2%) withdrew from the study, and four (2%) were wrongly included (did not use Tac), resulting in 100 evaluable patients in Group A1 and 95 in A2. Between October 2014 and August 2015, 144 patients attended the 1-year routine investigation at the transplant centre, 23 did not meet the inclusion criteria (10 not on Tac, six not managed their own medications, seven did not understand Norwegian/English), and 18 were not consider for inclusion (closed research laboratory), giving a total of 103 eligible for inclusion. Three patients refused participation, resulting in 100 included patients in Group B (Fig. 2). Baseline characteristics for nonincluded patients were comparable to included patients [age, sex, donor type, dialysis time (data not shown)].

Baseline and 1-year characteristics for Group A and B are listed in Table 2 [and supplementary content (SC) Table S1]. A higher percentage used Tac once-daily formulation at 1 year in Group B ($P < 0.001$) than in Group A, and the BPAR rate was higher and more patients had developed dnDSA in Group B as compared with Group A. Within Group A, significantly more patients had been switched to once-daily Tac in the A2 subgroup during the 1-year follow-up ($P = 0.003$).

BAASIS©

BAASIS© response rate was 87% at 8 weeks (Group A) and 82% at 1 year (76% in Group A and 87% in Group B). Overall, 68% of the patients answered the questionnaire online. Nonresponders of BAASIS© at 1 year were significantly younger (51 ± 15 vs. 56 ± 14 years, $P = 0.013$), more were first-transplant recipients (96% vs. 85%, $P = 0.032$) and fewer were pre-emptively transplanted (15% vs. 37%, $P = 0.003$).

Suboptimal implementation of the IS medications was the only reason for nonadherence. None of the patients reported drug holidays, self-induced dose changes or discontinuation. In Group A, 9% of patients at 8 weeks and 32% at 1 year were defined as NoAd according to the overall BAASIS© assessment. At 8 weeks, 4% had missed at least one dose (taking nonadherence) while 5% took all doses but had a deviation from prescribed time (timing nonadherence; Table 3). There was no significant difference in taking nonadherence from 8 weeks to 1 year, 4% vs. 7% ($P = 0.210$), while the timing nonadherence increased significantly from 5% to 25% ($P < 0.001$).

At 1 year (pooled Group A and B), 29% had suboptimal implementation of the IS medications according to BAASIS©; 7% had missed a dose while 22% failed only in timing. Half of the patients that missed a dose also had a time deviation.

Fortnightly BAASIS© investigations in the early post-transplant phase and around the 1-year investigation, in addition captured 5% taking and 8% timing nonadherence in the early post-transplant phase (Group A1), and 4% taking and 6% timing nonadherence at 1 year (SC Table S2). Intensive assessment (Group A1) as compared with single assessment (Group A2) did not influence adherence either at 8 weeks or 1 year after transplantation (SC Table S5). The response rate of BAASIS© decreased some with repeated measurements

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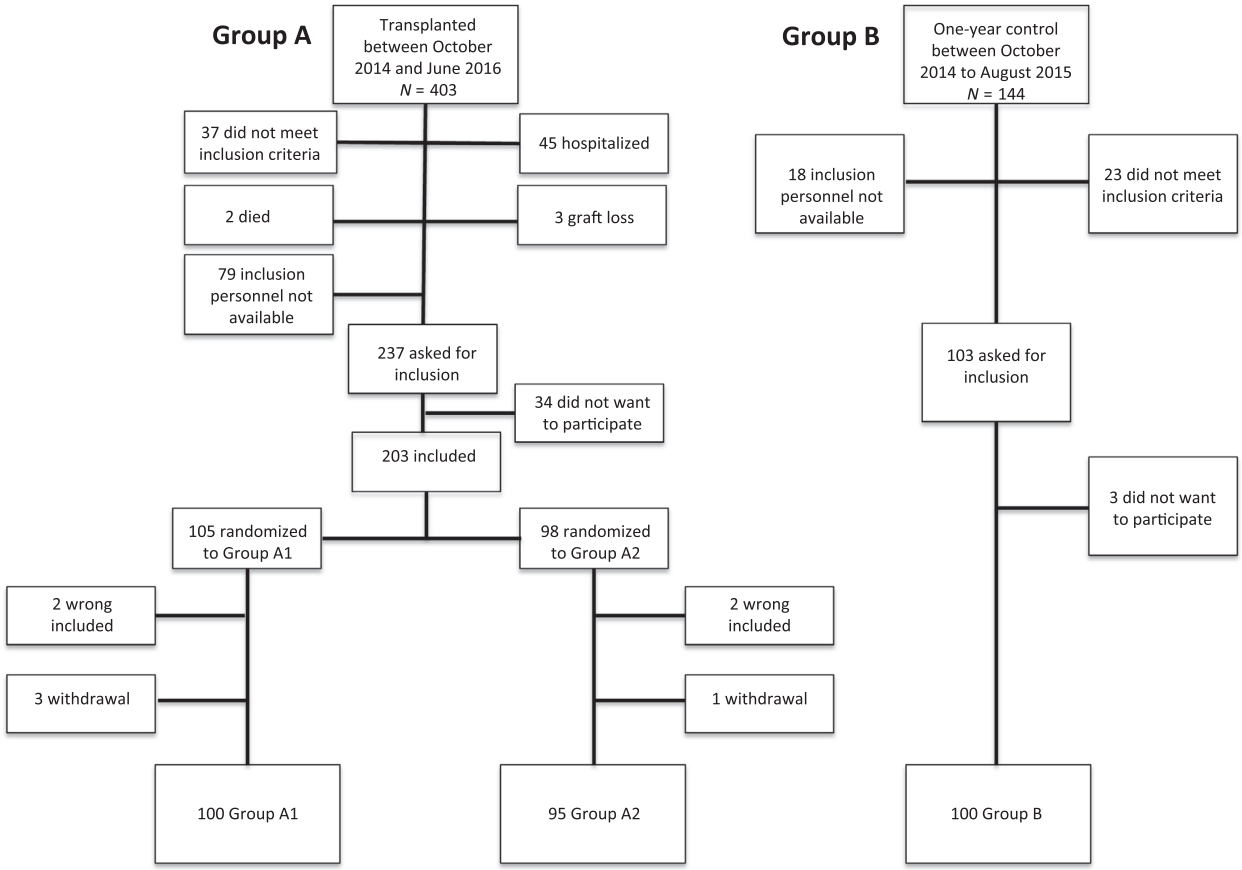

Figure 2 Flow chart for inclusion of patients in Group A (left) and Group B (right).

in the frequent assessment group, and was highest at the 4-weeks and 1-year assessment.

Clinician′s score

Valid data from clinician′s score of adherence were obtained for 99% of the patients at 8 weeks and 88% at 1 year. The nonadherence prevalence tended to increase from 8 weeks (3%) to 1 year (7%) in Group A ($P = 0.23$).

Tac variability

In association to the 8-week and 1-year investigation, 92% and 88%, respectively, had valid Tac data for assessment of its variability.

None of the Tac-concentrations indicated discontinuation of IS medication. The prevalence of nonadherence to the Tac treatment was therefore in the implementation phase.

Patients defined as NoAd, by any of the other tools, did not have a higher TacVar (SC Table S3).

Tablet count

Accurate tablet count was evaluable in 43% of patients (Group A1). These data were hence not included in further analyses. The reason for incomplete tablet counts was patients forgetting to bring all IS medications to the visits.

Combination of tools

BAASIS©, clinician′s score and TacVar showed only weak pairwise agreement (Table 4). At 1 year, the different tools identified to a large extent different patients as NoAd, as the nonadherence overlap between the different tools was low (SC Table S4). Depending on the combination of tools, the 1-year nonadherence prevalence ranged from 7% to 38% (Table 5).

Comparison of subgroups

There was no significant difference in prevalence of nonadherence at 8 weeks or 1 year according to any of

Table 2. Patient characteristics.

	All included (*N* = 295)	Group A (*N* = 195)	Group B (*N* = 100)	A vs. B
Age at time of transplant, years (SD)	55 (14)	55 (14)	53 (14)	*P* = 0.198*
Male sex, *n* (%)	216 (73)	140 (71)	76 (75)	*P* = 0.484†
First transplant, *n* (%)	259 (87)	171 (87)	88 (87)	*P* = 0.977†
Pre-emptive transplantation, *n* (%)	100 (34)	66 (34)	34 (34)	*P* = 0.999†
Living donor, *n* (%)	92 (31)	59 (30)	33 (33)	*P* = 0.650†
HLA AB-DR mismatch (SD)	3.0 (1.4)	3.1 (1.4)	2.9 (1.4)	*P* = 0.144*
Cold ischaemia time, h (SD)	10.1 (6.1)	10.0 (6.2)	10.3 (6.1)	*P* = 0.821*
Panel reactive antibodies ≥20%, *n* (%)	7 (3)	4 (2)	3 (3)	*P* = 0.702†
P-Creatinine, μmol/l (SD)				
8-weeks		133 (85)		
1-year	120 (38)	122 (41)	116 (32)	*P* = 0.177*
mGFR, ml/min/1.73^2 (SD)				
8-weeks		57 (14)		
1-year	58 (15)	57 (15)	60 (14)	*P* = 0.070*
Tacrolimus C_0, μg/l (SD)				
8-weeks		6.5 (1.4)		
1-year	6.3 (1.8)	6.2 (1.8)	6.4 (1.8)	*P* = 0.214*
Tacrolimus variability, CV% (SD)				
8-weeks		14 (6)		
1-year	17 (12)	17 (13)	17 (10)	*P* = 0.943*
Once-daily tacrolimus formulation, *n* (%)				
1-year	125 (42)	90 (48)	28 (28)	*P* < 0.001†
Twice-daily tacrolimus formulation, *n* (%)				
1-year	163 (55)	97 (52)	72 (72)	*P* < 0.001†
Development of dnDSA by 1 year	20 (7)	9 (5)	11 (11)	*P* = 0.039†
BPAR rate by 1 year	31 (11)	15 (8)	16 (16)	*P* = 0.028†

BPAR, biopsy proven acute rejection rate; dnDSA, *de novo* donor-spesific antibodies; mGFR, measured glomerular filtration rate; SD, standard deviation.

Patient characteristics for Group A1 and A2: supplementary content Table S1.

*Comparison of Group A and B using independent sample *T*-test.

†Comparison of Group A and B using chi-square or Fisher exact test.

Table 3. Percentage of nonadherence using different adherence tools at 8 weeks and 1 year.

	Group A Nonadherence		Group B Nonadherence
Tools	8-weeks (%)	1-year (%)	1-year (%)
BAASIS©	9*	32*	23
Timing dimension	5*	25*	18
Taking dimension	4	7	5
Clinician's score	3	7	12
Tac variability	3*	13*	11

Tac, tacrolimus.

*Indicate significant difference ($P < 0.05$) between 8 weeks and 1 year in Group A using McNemar's test.

the tools or combination of tools between Group A1 and A2, or between Group A and B.

Females had lower odds of being NoAd when assessed by TacVar (OR 0.114; confidence interval [CI] 0.034, 0.621; $P = 0.009$). Age, Tac formulation, donor type, transplantation number or dialysis before transplantation, were not found to be predictors for nonadherence with any of the tools.

1-year clinical outcomes

A total of four patients in Group A experienced isolated GL (2.1%) and three patients died (1.5%) during the first post-transplant year. The overall BPAR rate was 11% and 7% developed dnDSA, not significantly different between Group A1 and A2 ($P = 0.71$ and $P = 0.74$).

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Table 4. Agreement between the different adherence tools.

Tool combinations	Cohen's kappa	
	8-weeks	1-year
BAASIS© Clinician's score	0.166*	0.143*
BAASIS© Tac variability	0.137*	0.124*
Clinician's score Tac variability	0.383**	0.147*

Tac, tacrolimus.

*The result is significant with *P*-value 0.05 or less (2-tailed).

**The result is significant with *P*-value less than 0.01 (2-tailed).

Table 5. Percentage of nonadherence using different tools and tool combinations at 1 year (pooled Group A and B).

Tools/tool combinations	Nonadherence 1-year (%)
BAASIS©	29
Timing dimension	22
Taking dimension	7
Clinician's score	9
Tac variability	12
BAASIS© + clinician's score	32
BAASIS© + clinician's score + Tac variability	38

Tac, tacrolimus.

Most BPARs were discovered in protocol biopsies at 8 weeks and 1 year.

The development of dnDSA and BPAR rate was numerically lower (Table 6) and mGFR higher (Table 7) in Ad patients, but not significantly different from NoAd patients. In the Cox regression analysis (SC Tables S6 and S7), nonadherence, as determined by BAASIS©, increased the hazard of development of dnDSA with a factor of 2.70 (CI 1.07, 7.13).

Discussion

With a total response rate of over 80% and about two-thirds of the BAASIS© data delivered electronically, it seems plausible to include this in a quality register. Both clinician's score and TacVar are also implementable with standard data capture processes in such registries. Different adherence tools captured to a large degree different patients, so in line with previous studies the current data support the use of combination of tools [13,20]. The present data also indicate that repeated self-assessment, for example obtaining BAASIS© forms fortnightly, identifies additional and different patients compared with a single assessment, but did not *per se* influence patients adherence. Two to three fortnightly self-reported adherence assessments submitted electronically should be considered when used in a quality registry.

Table 6. Adherence status and the frequency of *de novo* donor-specific antibodies and biopsy-proven acute rejection rate the first year after transplantation.

Tools	dnDSA, *n* (%)	BPAR, *n* (%)
BAASIS©		
Adherent	8 (5)	15 (9)
Nonadherent	8 (12)	13 (19)
Timing dimension		
Adherent	9 (5)	18 (10)
Nonadherent	7 (12)	8 (13)
Taking dimension		
Adherent	15 (7)	23 (10)
Nonadherent	1 (6)	5 (31)
Clinician's score		
Adherent	14 (6)	23 (10)
Nonadherent	2 (9)	4 (18)
Tac variability		
Adherent	16 (7)	23 (10)
Nonadherent	0 (0)	4 (13)

BPAR, biopsy-proven acute rejection rate; dnDSA, *de novo* donor-specific antibodies; Tac, tacrolimus.

Data presented as frequency (with percentage) of patients developed dnDSA and BPAR.

As expected, discontinuation of IS medication was not a problem. Overall the present study showed that nonadherence was because of suboptimal implementation of the IS medications the first post-transplant year. Self-reported nonadherence using BAASIS© in this population was 29% at 1-year, which is in line with previous studies [24,29,35]. As other reports also have shown [36,37], the majority of these NoAd patients took all the prescribed doses but had a time deviation (22%). A 2-h time deviation as the BAASIS© form defines as nonadherence may seem rigid and its clinical relevance in RTxR has been questioned [38,39]. Recent pharmacokinetic simulation data indicate that ±4 h may be more relevant [40]. However, self-reported adherence is often underreported [17,41,42], which may advocate for continuing the use of ±2 h. To our knowledge, there are no data comparing 2- vs. 4-h time windows on long-term outcomes.

Table 7. Measured glomerular filtration rate 1-year after transplantation in different adherent and nonadherent patients.

Tools	mGFR, ml/min/1.73^2 (SD)	Adherent versus nonadherent
BAASIS©		
Adherent	58 (14)	$P = 0.154$
Nonadherent	54 (17)	
Timing dimension		
Adherent	57 (15)	$P = 0.417$
Nonadherent	55 (16)	
Taking dimension		
Adherent	57 (15)	$P = 0.195$
Nonadherent	52 (18)	
Clinician's score		
Adherent	58 (15)	$P = 0.889$
Nonadherent	58 (13)	
Tac variability		
Adherent	58 (15)	$P = 0.850$
Nonadherent	57 (14)	

mGFR, measured glomerular filtration rate; SD, standard deviation.

Calculated using Independent sample *T*-test on log-transformed data.

Nonadherence can trigger development of dnDSA [11,43], which have been associated with poor outcome [44,45]. Nonadherence, as determined by BAASIS©, significantly increased the hazard of developing dnDSA in the current Cox regression analysis. However, there may be some bias with regards to the rate of dnDSA and BPAR in Group B, as it only consist of patients actually meeting at the transplant centre for their 1-year control.

Once-daily Tac formulation has been suggested to improve adherence [46]. However, in the present study patients using once-daily formulation did not show better adherence at 1 year in any of the utilized tools. Given the high pill burden for this population, the switch to once-daily formulation will not reduce the daily dosing times, as other immunosuppressants, like MMF, are administered twice daily [47].

More frequent BAASIS© assessment identified additional NoAd patients, indicating that nonadherence is not necessarily a constant behaviour. However, it is important not to overload the patients with too frequent adherence assessment, as this decreased the response rate on self-reported adherence. In registries, one should consider repeating self-reported adherence tools at least once, maybe even twice, within a reasonable short time frame for annual capture of adherence. When using electronic delivery of the forms, this should be applicable.

Tablet count was not fulfilled in the study, and was surprisingly difficult to include in a clinical outpatient setting. Patients forgot, or refused, to bring all their blister, and data quality was not good enough to be included in the analyses. In our experience, tablet count was hence not a tool that can be implemented in real life.

We only observed a weak agreement between the different adherence tools, with little overlap between nonadherence evaluations. BAASIS© and clinician's score capture adherence of the whole IS regimen, while TacVar only capture adherence to Tac treatment, which may be one reason for the low correlation between the tools. The tools should therefore not be used alone. It should also be noticed that the clinician's score is likely the least useful measure, especially at 1 year, because of the relatively limited interaction between patients and clinicians in that phase. In addition, the clinician will probably base the score on communication with the patient and on the Tac-concentrations, both of which are captured by other tools. When using BAASIS© in combination with clinician's score and TacVar, about one-third of all patients seem to be nonadherent to IS medications.

The main strength of the present study is that it was performed in a real-life setting, in a large Norwegian cohort of RTxR. Also, paired data from several adherence tools were investigated both in the early post-transplant phase as well as 1-year after transplantation with patients being their own controls. This assures no survivor selection bias. The limitations of the study were first of all that it is not possible to rule out a certain degree of participant selection bias, as NoAd patients are more likely to refuse study participation. Second, relatively few concentrations were available for calculation of TacVar at 1 year, as patients usually only meet monthly at their local nephrologists in this time period. Third, electronic tablet count solution would have been favourable, but this was unfortunately not possible to implement in the present study. Finally, this is a study performed during the first post-transplant year and may not reflect the patient's overall IS medication intake behaviour during later years. A recently published Norwegian study using BAASIS© during later post-transplant years showed a higher nonadherence prevalence [48]. During the 1-year follow-up, the present study did not demonstrate a worsening in renal function or AR in NoAd patients. The study was however not powered for this, and a previous study with longer follow-up has demonstrated this [49]. Inclusion of adherence data in a national quality registry can help

identify high-risk patients and open up for evaluating prospective intervention studies to improve adherence in specific populations in a proper way. Further studies should focus on implementation of adherence-promoting interventions [22,50].

Conclusion

BAASIS© and clinician's score are both applicable for annual capture of adherence data in RTxR. They are low in cost, user-friendly and easy to carry out on an annual basis. As TDM of Tac already is a part of routine clinical practice in RTxR, TacVar as a measure of adherence is also applicable. All tools can be incorporated in a national quality registry, and when used in combination they can identify potentially high-risk patients.

Authorship

MTG, KM, KL, AVR, MHA, SDG and AÅ: designed the study. MTG, KM, KL, TJ, AH and AÅ: collected the data. MTG, KM and AÅ: did data analysis and wrote the article, whereas all authors have been involved in the discussion of results, and have contributed to, read and approved the final article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patient characteristics for patients in Group A randomized to A1 or A2.

Table S2. BAASIS© taking and – timing nonadherence at the single time-point answer of BAASIS© at 8 weeks and 1 year, compared with fortnightly answers in the same period.

Table S3. Comparison of median tacrolimus variability in adherent and nonadherent patients at 8 weeks (Group A) and 1 year (pooled Group A and B).

Table S4. Overlap of adherent and nonadherent patients using different combinations of adherence tools at 1 year (pooled Group A and B).

Table S5. Comparison of nonadherence in Group A1 and A2 at 8 weeks and 1 year using different adherence tools.

Table S6. Results from Cox regression analysis with development of *de novo* donor-specific antibodies as outcome variable and adherence as a time-dependent variable.

Table S7. Results from Cox regression analysis with biopsy-proven acute rejection as outcome variable and adherence as a time-dependent variable.

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