







ORIGINAL ARTICLE

# Is simplification of immunosuppressive medication a way to promote medication adherence of kidney transplant recipients? Findings from a randomized controlled trial

ESOT 2021  
MILAN  
IN-PERSON & ONLINERegina van Zanten , Annelies de Weerd , Michiel Betjes ,  
Mariëken Boer-Verschagen & Emma K. Massey 

Department of Internal Medicine,  
Erasmus MC Transplant Institute,  
University Medical Center Rotterdam,  
Rotterdam, The Netherlands

## Correspondence

Emma K. Massey, Department of  
Internal Medicine, Nephrology and  
Transplantation, RG-5,  
P.O. Box 2040, 3000 CA Rotterdam,  
The Netherlands.  
Tel.: \*3110704607;  
e-mail: e.massey@erasmusmc.nl

## SUMMARY

After kidney transplantation, a strict immunosuppressive medication regimen is necessary for graft survival. However, nonadherence to medication has been shown to occur early after transplantation and to increase over time. Weaning the recipient off dual therapy onto monotherapy in order to reduce immunosuppressive burden may also be a way to promote adherence, although little is known about the impact of such a regimen on fear of rejection. We performed a cohort study on medication adherence and fear of rejection in a randomized, investigator-driven, open-label, single-centre pilot study. Recipients were randomized at 6-months post-transplant to either continue Tacrolimus and Mycophenolate mofetil (TAC/MMF) or to taper MMF at 6 months and discontinue MMF at 9 months (TAC monotherapy). Recipients completed questionnaires about medication adherence and fear of rejection at 6 and 12-months post-transplantation. Medication adherence was significantly higher in the TAC monotherapy group compared to dual TAC/MMF therapy group ( $\chi^2(1) = 4.582$ ;  $P = 0.032$ ). We found no difference in fear of rejection between the two groups of recipients ( $P = 0.887$ ). Simplification of the medication regimen is a potential tool for increasing adherence in clinical practice (Netherlands Trial Register – NL4672).

*Transplant International* 2021; 34: 1703–1711

## Key words

fear about rejection, graft rejection, kidney transplantation, medication adherence, tacrolimus

Received: 17 June 2021; Revision requested: 15 July 2021; Accepted: 15 July 2021

## Introduction

### Background and objectives

After kidney transplantation, a strict medication regimen of immunosuppressive medication is necessary for

graft and patient survival. Before and after transplantation, transplant recipients receive education about the importance of taking the medication. Despite this information, nonadherence to medication frequently occurs [1]. If possible and safe, conversion of the medication regimen to monotherapy could be a strategy to improve

adherence. However, it is unclear what psychological impact simplification of the regimen may have on recipients, for example, on fear of rejection.

The World Health Organization (WHO) defined adherence as 'the extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider' [2]. Despite poorer clinical outcomes due to nonadherence [3], prevalence of nonadherence among kidney transplant recipients is estimated to be between 38% and 55% [4]. Recipients with declining adherence in the first months after transplantation had a significantly higher risk of more frequent and earlier acute rejection and higher death-censored graft loss up to 15-months post-transplant [5]. There are several possible causes for nonadherence, whereby the WHO has identified five dimensions; social and economic factors, health-care team and systems-related factors, therapy-related factors, condition-related factors and patient-related factors [2]. One of the therapy-related factors that may be a cause of nonadherence is the complexity of the medication regimen [2,6].

The majority of kidney transplant recipients worldwide are on a regimen with Tacrolimus (TAC), Mycophenolate mofetil (MMF) with or without prednisone. As MMF and many TAC formulations are dosed twice daily, most recipients use immunosuppressive medication twice daily at 12-h intervals. Previous research has examined the effect of the simplification of only TAC from a twice-daily to once-daily with inconclusive results. Some studies have demonstrated higher medication adherence after conversion to a once-daily TAC regimen [7–9]. For example, Kuypers *et al.* [8] found that, in once-daily TAC, a significantly higher percentage of recipients persisted with their medication regimen compared to the twice-daily TAC. Other studies found no significant difference between twice-daily and once-daily TAC regimens, but did find that quality of life was higher in a once-daily regimen [10,11]. This suggests that the patient perspective may differ when the regimen is simplified. In some of these studies, MMF was continued and in others, it was unclear whether MMF was discontinued. Only one study was found whereby the authors compared a small group of recipients with a once-daily immunosuppressive medication therapy with TAC and without MMF and recipients with a twice-daily therapy [12]. The preliminary results showed no significant difference between the groups on self-reported medication adherence. Further research on conversion to monotherapy on medication adherence in kidney transplant recipients is lacking.

After transplantation, many recipients experience challenges in emotional adjustment [13]. Anxiety after transplantation can have several causes, for example, coping with a new lifestyle and adjustments to threats of infections, rejection and malignancies [14]. Recipients often report fear of rejection after transplantation, and some recipients even report that the fear of rejection is the worst stress factor after transplantation [15,16]. On the one hand, the medication regimen may generate or exacerbate fear, whereby the fact that recipients' need to take medication twice a day acts as a reminder of possible rejection [16]. On the other hand, weaning recipients off immunosuppression could also trigger fear of rejection due to concerns regarding the effectiveness of the reduced dose to suppress an immune reaction. There has been little investigation about the impact of the simplification of the medication regimen from dual to monotherapy on the level of fear of rejection.

Satisfaction with the medication regimen can contribute to medication adherence [17]. Conversion to monotherapy results in less pills to take for the recipients. It might be expected that the fewer medicine a recipient needs to take, the more satisfied the recipient would be with the medication regimen and the more adherent. However, it could also be possible that taking more medication to prevent rejection and taking it twice a day can give the recipient a feeling of control. In that case, simplifying the medication could cause reduced satisfaction with the regimen and could increase fear of rejection. It is also of interest if conversion to TAC monotherapy has an effect on the experienced side-effects. It is thus unclear how the conversion to monotherapy will impact satisfaction with the amount of medication and the experienced side-effects.

The current study is part of the TACmono study, which investigated outcomes after discontinuing MMF in TAC-treated kidney transplant recipients with immunological low-risk. The objective of the present study was to assess if conversion from dual therapy to monotherapy has an effect on self-reported medication adherence, fear of rejection, satisfaction and side-effects.

## Materials and methods

### Study design and procedure

This was a randomized, investigator-driven, open-label, single-centre pilot study in a University Medical Center in the Netherlands with pre- (T0) and postintervention (T1) measures. Recipients were asked to complete two sets of questionnaires, at 6 and 12 months after kidney

transplantation. The questionnaires at 6 months were completed before randomization. Recipients completed the questionnaire at the outpatient clinic in the presence of a research nurse during the study visit. Recipients completed the questionnaires themselves, but if necessary, the nurse supported completion, for example, by clarifying the meaning of questions or reading them out loud. Recipients were informed that their treating physician would not have access to the results of the questionnaires.

### Participants

The target population in this study were adult kidney transplant recipients, who received a deceased or living donor kidney. In short, all consecutive immunological low-risk kidney transplant recipients with peak PRA <5% and <4 HLA mismatches on A, B and DR loci were asked for consent. The full in- and exclusion criteria are described in Table S1. All recipients switched at day 7 after transplantation from Prograf twice-daily to Advagraf once-daily. Prednisone was tapered to 5 mg after 3 months and discontinued at month 5.

Eligible recipients were included during admission for kidney transplantation. After a run-in period of 6 months, recipients were randomized to one of two study arms if they met the following randomization criteria: eGFR (CKD-EPI formula) >30 in ml/min  $\times$  1.73 m<sup>2</sup> with proteinuria  $\leq$ 50 mg/mmol creatinine in spot urine.

### Randomisation and intervention

Randomization took place on patient level at 6 months after transplantation, after completing the questionnaires. A consultant statistician made a randomization list, using a validated computer system that automates the random assignment of treatment groups to randomization numbers at a specific 1:1 ratio. The individual numbers were placed in sealed envelopes that were opened at the moment of patient randomization. Concealed allocation was ensured by having an independent researcher with no involvement in the study making the list and preparing the envelopes.

Recipients who met the inclusion criteria were randomized to either the intervention arm (TACmono) in which MMF was halved at 6 months and discontinued at 9 months or to the control group arm in which dual therapy (TAC/MMF) was continued. Targeted trough levels were 5–8 mg/l for TAC in both groups and 1.5–3.0 mg/l for MMF in the control group.

## Outcomes

### *Medication adherence*

Adherence to immunosuppressive medication was measured using the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS© interview) [18]. This scale consists of four questions about the previous 4 weeks on the taking and timing of medication, drug holidays, reduction of the dose and persistence, with the answer options 'Yes' (1) and 'No' (0). An affirmative answer to any of these questions qualifies a recipient as nonadherent. This scoring is intentional strict due to the assumption that recipients under-report nonadherence with a self-report questionnaire [19]. If the answer is 'yes' to any of the items, recipients are asked how often they were non-adherent.

### *Fear of rejection*

Fear of rejection was measured using the six-item 'intrusive anxiety' subscale of the Perceived Threat of the Risk for Graft Rejection (PTGR) questionnaire [15]. Items were scored on a 5-point Likert scale ranging from 'Strongly disagree' (1) to 'Strongly agree' (5). Internal consistency has been shown to be high, Cronbach's  $\alpha = 0.91$  [15]. The mean score is calculated, and a score of  $\leq 2$  is considered to be 'low', a mean score of 3 is considered 'uncertain', and a score of 4 or above is considered to be 'high' [15].

### *Satisfaction*

In order to explore the recipients subjective experience of the medication, two questions were developed on satisfaction with the amount of immunosuppressive medication needed to be taken and level of side-effects experienced. The items were rated on a 10-point Likert scale, whereby a higher score indicates greater satisfaction with the amount of medication needed to be taken and more experienced side-effects.

### *Covariates*

We extracted the following socio-demographic characteristics from the medical records: date of birth, ethnicity, educational level, organ type and marital status. Educational level was recoded into 'low', 'middle' and 'high', according to the format of the national office for statistics in the Netherlands (CBS) [20]. Ethnicity was

recoded into European and Non-European due to the small number of recipients per category.

### Sample size

The TACmono study was designed as a pilot study with feasibility criteria. Therefore, a classical sample size calculation did not apply, and the target of 120 included recipients was based on the recruitment rate, one of the feasibility criteria.

For the overall TACmono study, a Data Safety Monitoring Board (DSMB) was established. The interim analyses was performed after 40 randomized patients completed the study and the DSMB decided continuation of the study.

### Statistical methods

Socio-demographic variables and medical characteristics were described as frequencies (%), and a comparison was made between TAC/MMF – and TACmono group using a chi-square test or independent samples *t*-test. In addition, adherence level, fear of rejection and satisfaction at 6 and 12 months were described. The univariate analyses between TAC/MMF and TACmono group were conducted using nonparametric tests due to the fact that data of fear about rejection and satisfaction was not normally distributed. The univariate analysis for adherence was conducted on adherence versus nonadherence levels. How often recipients were nonadherent was not compared because of the small numbers per category. The transitions of medication adherence between TAC/MMF and TACmono group at 6 and 12 months after transplantation were described and compared using chi-square. Multilevel regression analyses was used to test the difference at 12 months between the TAC/MMF and TACmono group, while controlling for socio-demographic and medical variables. Logistic regression was used for the outcome adherence and linear regression for fear of rejection.

## Results

### Patient population

Between August 2014 and April 2018, 121 recipients were included in the main study. After the run-in period of 6 months, 79 recipients met the randomization criteria and were randomized to either TACmono ( $n = 38$ ) or TAC/MMF ( $n = 41$ ), see flowchart Fig. 1. In the TAC/MMF group, one recipient did not fill in

the questionnaires due to a language barrier and was therefore extracted from the analysis. In the period after randomization ( $n = 78$ ), six recipients dropped out because of, two in the TAC/MMF group and four in the TACmono group. All these data were included in the analysis according to the intention-to-treat principle, see flowchart.

The majority of the recipients were male (73.1%), European (69.9%), had a low level of education (56.2%) and had a median age of 61.5 years. More than the half of the recipients had a living donor (59.0%), see Table 1.

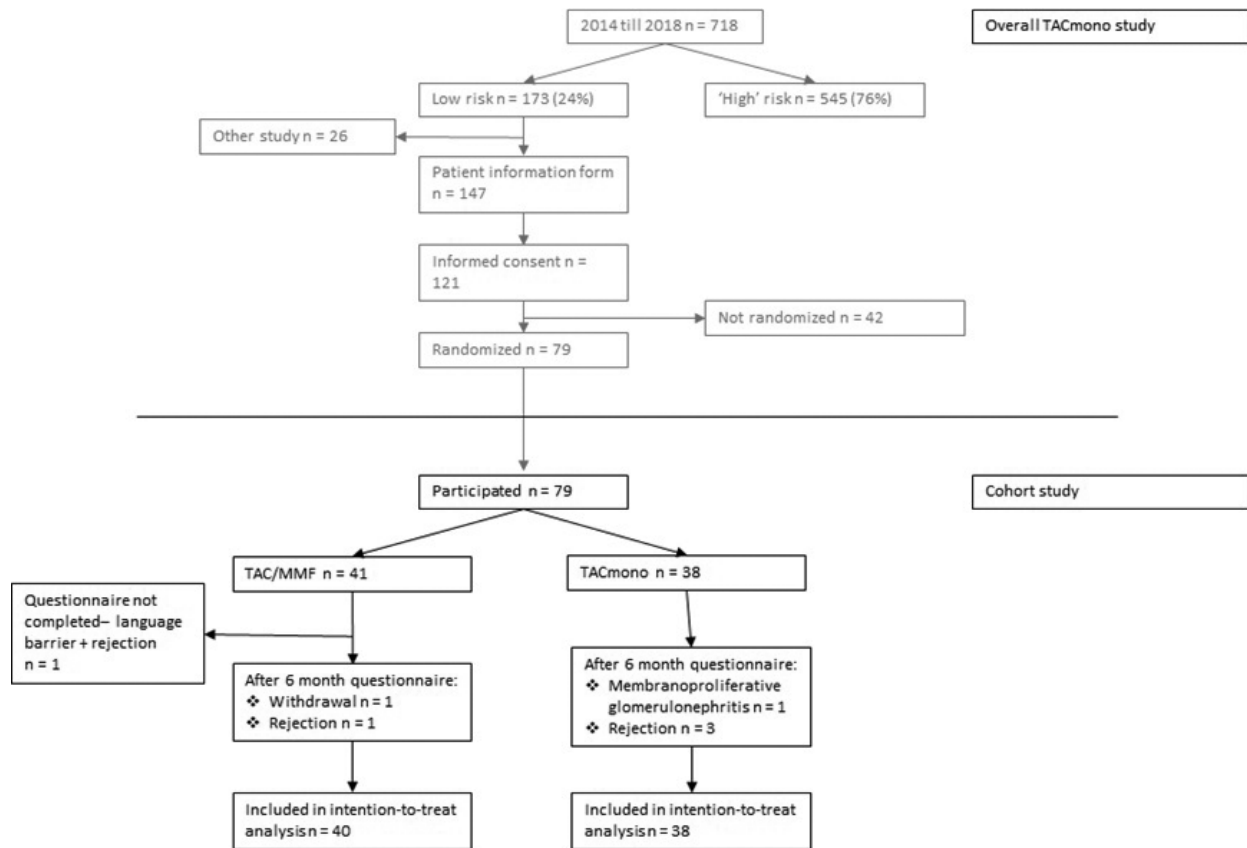
### Medication adherence

At 6 months, 40.5% of the participants in the TAC/MMF group reported being nonadherent (overall), and in the TACmono group, 21.6% reported being nonadherent, see Table 2. This difference was not significant ( $\chi^2 (1) = 3.091$ ;  $P = 0.079$ ). Table 2 shows that 12 months after transplantation, 50% of the recipients in the TAC/MMF group were nonadherent. This was significantly more than recipients in the TACmono group (25%) ( $\chi^2 (1) = 4.582$ ;  $P = 0.032$ ). The absolute difference was 25% (95% CI 3.14–46.86%) and relative effect was 50% (95% CI 25–99%). In addition, recipients in the TAC/MMF group reported more often to have missed a dose (type ‘taking’) than recipients in the TACmono group ( $P = .031$ ). Table 3 shows the logistic regression on medication adherence controlling for the socio-demographic and medical characteristics. Recipients with a middle educational level were significantly more nonadherent compared to recipients with a high educational level, controlled for the other variables (see Table 3). While controlling for socio-demographic and medical variables, we found a trend towards greater nonadherence in the TAC/MMF group at 12 months compared to the TACmono arm ( $P = 0.057$ ).

Figures 2 and 3 show the transitions of medication adherence between TAC/MMF and TACmono group at 6 and 12 months after transplantation. The figures show that a greater proportion of the TAC/MMF group were nonadherent and remained so, plus a higher proportion in this group transitioned from adherent at baseline to nonadherent at follow-up compared to the TACmono group.

### Fear of rejection

Table 2 shows the mean scores for the intrusive anxiety scale of the PTGR. The median scores for all time



**Figure 1** Flowchart of this study.

**Table 1.** Descriptive characteristics of kidney transplant recipients 6 months after transplantation.

	Total (n = 78)	TAC/MMF group (n = 40)	TACmono group (n = 38)	P
Age				
Median (IQR)	61.50 (55.8–68.0)	60.50 (56.0–69.0)	62.50 (52.8–67.0)	0.497
Sex				
Male (%)/female (%)	57 (73.1)/21 (26.9)	28 (70.0)/12 (30.0)	29 (76.3)/9 (23.7)	0.530
Ethnicity	N = 73	N = 37	N = 36	
European (%)/non-European (%)	51 (69.9)/22 (30.1)	27 (73.0)/10 (27.0)	24 (66.7)/12 (33.3)	0.557
Caucasian/European (%)	51 (69.9)	27 (73.0)	24 (66.7)	
Asian (%)	9 (12.3)	4 (10.8)	5 (13.9)	
African (%)	6 (8.2)	3 (8.1)	3 (8.3)	
Turkish (%)	5 (6.8)	2 (5.4)	3 (8.3)	
Other (%)	2 (2.7)	1 (2.7)	1 (2.8)	
Educational level	N = 73	N = 37	N = 36	
Low (%)	41 (56.2)	23 (62.2)	18 (50.0)	0.576
Middle (%)	18 (24.7)	8 (21.6)	10 (27.8)	
High (%)	14 (19.2)	6 (16.2)	8 (22.2)	
Marital status	N = 75	N = 37	N = 38	
Married/living together/partnership (%)	53 (70.7)	29 (72.5)	24 (63.1)	0.148
Single/divorced/widowed (%)	22 (29.3)	8 (20.0)	14 (36.9)	
Organ type	n = 78	N = 40	N = 38	
Living (%)	46 (59.0)	22 (55.0)	24 (63.2)	0.464
Deceased (%)	32 (41.0)	18 (45.0)	14 (36.8)	

**Table 2.** Descriptive statistics of outcome variables – 6 and 12 months.

	TAC/MMF group	TACmono group	<i>P</i>	TAC/MMF group	TACmono group	<i>P</i>
	T0 (6 months)			T1 (12 months)		
Medication adherence – overall	<i>N</i> = 37	<i>N</i> = 37	0.079	<i>N</i> = 38	<i>N</i> = 32	0.032
Adherent (%)	22 (59.5)	29 (78.4)		19 (50.0)	24 (75.0)	
Nonadherent (%)	15 (40.5)	8 (21.6)		19 (50.0)	8 (25.0)	
Medication adherence – taking	<i>N</i> = 40	<i>N</i> = 38	0.088	<i>N</i> = 38	<i>N</i> = 32	0.031
Adherent (%)	32 (80.0)	36 (94.7)		28 (73.7)	30 (93.8)	
Nonadherent (%)	8 (17.5)	2 (5.2)		10 (26.3)	2 (6.3)	
One time (%)	5 (12.5)	1 (2.6)		9 (23.7)	1 (3.1)	
Two times (%)	2 (5.0)	1 (2.6)		0 (0.0)	1 (3.1)	
Three times (%)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Four or more times (%)	0 (0.0)	0 (0.0)		1 (2.6)	0 (0.0)	
Missing (%)	1 (2.5)					
Follow-up question – drug holiday	<i>N</i> = 7	<i>N</i> = 2	1.00	<i>N</i> = 9	<i>N</i> = 2	1.00
No (%)	6 (85.7)	2 (100.0)		8 (88.9)	2 (100%)	
Two times (%)	1 (14.3)	0 (0.0)		1 (11.1)	–	
Medication adherence – timing	<i>N</i> = 37	<i>N</i> = 37	0.407	<i>N</i> = 38	<i>N</i> = 33	0.196
Adherent (%)	27 (73.0)	30 (81.1)		26 (68.4)	27 (81.8)	
Nonadherent (%)	10 (27.0)	7 (18.9)		12 (31.5)	6 (18.2)	
One time (%)	7 (18.9)	3 (8.1)		9 (23.7)	5 (15.2)	
Two times (%)	3 (8.1)	4 (10.8)		1 (2.6)	1 (3.0)	
Three times (%)	0 (0.0)	0 (0.0)		1 (2.6)	0 (0.0)	
Four or more times (%)	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)		
Intrusive anxiety				<i>N</i> = 34	<i>N</i> = 31	
Median (IQR)	2.00 (1.2–2.7)	1.33 (1.0–2.3)	0.198	1.33 (1.0–2.2)	1.33 (1.0–2.0)	0.887
Satisfaction amount of medication						
Median (IQR)	9.00 (7.0–9.0)	9.00 (7.0–10.0)	0.865	9.00 (7.0–10.0)	10.00 (9.0–10.0)	0.044
Amount of side-effects						
Median (IQR)	2.00 (1.0–7.0)	3.00 (1.0–7.0)	0.736	1.00 (1.0–3.75)	1.00 (1.0–4.0)	0.586

IQR, interquartile range; T0, pre-intervention measure; T1, postintervention measure; TAC/MMF, Tacrolimus and Mycophenolate mophetil therapy; TACmono, tacrolimus monotherapy.

points and both groups were  $\leq 2$ , which means that the scores can be interpreted as 'low'. In the univariate analysis, there were no significant differences between TAC/MMF and TACmono group at 6 and 12 months. The linear regression, as shown in Table 3, shows a significant relationship at 12 months between ethnicity and intrusive anxiety. Recipients who were Non-European reported significant more fear of rejection. No significant difference was found at 12 months between the TAC/MMF and TACmono group in this multivariate analysis.

### Satisfaction

Table 2 shows the results for the two satisfaction questions. Six months after transplantation, there were no differences between the groups on satisfaction with amount of medication and experienced number of side-

effects. At 12 months, the recipients in the TACmono group were more satisfied with the amount of medication than the TAC/MMF group. At 12 months, we did not find a difference between medians of the TAC/MMF and TACmono group regarding the number of side-effects experienced.

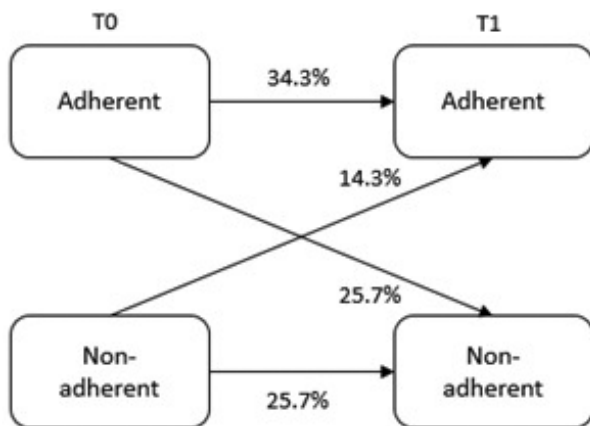
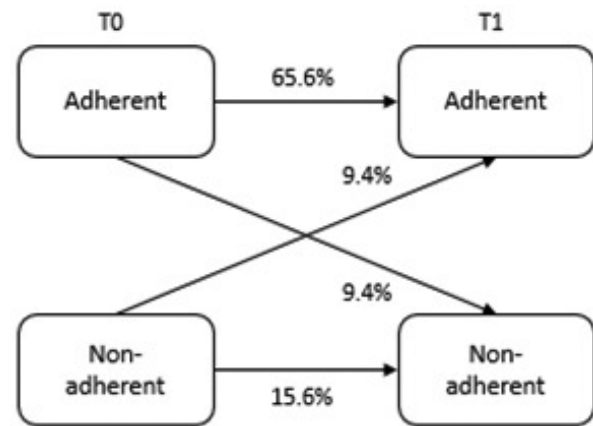
### Discussion

In this randomized controlled study, we gained insight into the impact of weaning recipients off immunosuppression in stable immunologically low-risk kidney transplant recipients on self-reported medication adherence, fear of rejection and satisfaction with their medication regimen. The main finding was that recipients with TACmono therapy were more likely to adhere to their medication regimen compared to recipients with dual TAC/MMF therapy. Exploration of the transitions



**Table 3.** Multiple regression analyses per outcome.

	Model $\beta$ (SE)	Model OR (95% CI)	P value
Medication adherence – logistic regression			
Constant	−2.409 (1.748)		0.168
Age	0.027 (0.026)	1.027 (0.976–1.080)	0.300
Sex (female)	−0.832 (0.656)	0.435 (0.120–1.573)	0.204
Ethnicity (European)	−0.231 (0.647)	0.794 (0.223–2.824)	0.721
Educational level (high)	Ref.		0.040
Educational level (low)	0.359 (0.826)	1.432 (0.284–7.229)	0.664
Educational level (middle)	2.039 (0.941)	7.680 (1.215–45.528)	0.030
Marital status (married, living together, partner)	−0.659 (0.675)	0.517 (0.138–1.941)	0.329
Organ type (living)	−0.121 (0.605)	0.886 (0.271–2.900)	0.842
Randomization	1.176 (0.617)	3.240 (0.967–10.853)	0.057
Fear of rejection – linear regression			
Constant	1.017 (0.791)		0.204
Age	0.008 (0.011)		0.473
Sex	−0.203 (0.296)		0.495
Ethnicity	0.670 (0.305)		0.033
Educational level	0.028 (0.173)		0.873
Marital status	0.257 (0.304)		0.402
Organ type	0.289 (0.280)		0.306
Randomization	0.084 (0.266)		0.755

**Figure 2** Transition medication adherence in recipients on Tacrolimus and Mycophenolate mofetil – between 6 and 12 months after kidney transplantation.**Figure 3** Transition medication adherence in recipients on tacrolimus monotherapy – between 6 and 12 months after kidney transplantation.

between groups indicated that maintenance of adherence over time was higher in the TACmono therapy group than the dual TAC/MMF therapy group. A possible explanation could be that, in this group, the medication burden decreased after converting to monotherapy [8]. As Tacrolimus was administered once daily in this study, recipients had a once-daily immunosuppressive medication regimen in the experimental

group after discontinuing MMF. Research has shown that recipients adhere more to their morning dose compared to the evening dose [21,22]. Mornings in general have more routine activities that could serve as a reminder for taking the medication [8], and recipients would be less likely to forget their medication as a result. Another possible explanation is that, for the experimental group, the risk of rejection could be higher because

of discontinuing of the MMF. Recipients in the TAC-mono group could therefore be even more alert to take their TAC and thus be more adherent. While greater vigilance is plausible, this did not appear to have developed into anxiety as fear of rejection was low in general and remained low regardless of changes in the regimen. Another possible explanation for lower rates of nonadherence is a more positive appraisal of the regimen. This aligns with the finding that recipients in the TAC-mono group were more satisfied with the (lower) amount of medication.

### Strengths and limitations

The overall strength of this study is the randomized controlled study design. We were able to compare a TAC/MMF and a TACmono group on medication adherence, fear of rejection and satisfaction with the medication regimen. A previous pilot study performed a study about the safety and adherence to a once-daily immunosuppressive regimen [12]. However, to our knowledge, this is the first randomized controlled trial that gave insight into the behavioural and psychological effects of conversion from dual to monotherapy in kidney transplant recipients.

We also must emphasize that the conversion to monotherapy was made in the context of a study. Recipients were provided with extensive information about the objectives of the study and were regularly monitored. The recipients may feel safe because of these regular check-ups. To what extent the results would be comparable outside a study is unclear and requires further investigation, in case conversion to monotherapy appears to be safe and will become the standard care for immunological low kidney transplant recipients. We recommend to integrate the same safety safeguard into standard care as in the study, for example, regular monitoring.

Another strength is the inclusion of a representative sample of our transplant population with regard to education; over half had a low level of education. In most research, recipients who cannot read or write are often excluded even though they are required to self-manage and adhere to medication after transplantation. Moreover, those with low literacy skills often have lower self-management skills to manage their medication regimen [23]. In order to promote participation of patients with lower education and potentially lower literacy skills and health literacy skills [24], the research nurse was present to offer assistance in completing questionnaires when needed. This appears to have resulted in a study cohort

that was representative for our mixed demographic and literacy skilled transplant population.

### Practical implications and future research

With this study, we add conversion to monotherapy, provided that monotherapy is considered medically safe, to the adherence-promotion tool-box for professionals. This study was conducted among immunologically low-risk recipients using strict medical endpoints and a run-in period. Therefore, this study does not imply that conversion to monotherapy is a suitable treatment for all kidney transplant recipients to prevent medication adherence. The message of our study is that, if conversion to monotherapy is considered medically safe by the physician, it may also contribute positively to medication adherence.

We note that all such decisions about changes to the medication regimen can impact not only behaviour but also perceptions and experience of the treatment. Therefore, such simplification should also be carried out with attention to shared-decision making together with the patient. The results of this study give us one piece of the puzzle in improving medication adherence among KTRs, as therapy-related factors is just one of the five possible factors that influence nonadherence [2]. Therefore, further research is needed to explore which strategies in these other domains can help boost adherence. Further research is also needed to explore the long-term effects of the conversion to monotherapy on medication adherence as well as the potential benefits for specific groups such as among recipients with a history of non-adherence.

### Authorship

The principal investigator of the main study is MB. AdW, MB, MB-V and EM: contributed to the study protocol. MB-V: was the participating research nurse during data collection. RvZ: performed the data analysis and prepared the manuscript. All authors read and approved the final manuscript.

### Funding

This study was funded by the Erasmus MC, University Medical Center Rotterdam.

### Conflict of interest

The authors declare no conflict of interest.



## Acknowledgements

We would like to thank the recipients for participating in this study. We also would like to thank the research nurses for the contribution to this study and Judith Kal-van Gestel for the data management.

## SUPPORTING INFORMATION

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

**Table S1.** Inclusion and exclusion criteria.

## REFERENCES

- Dew MA, Posluszny DM, DiMartini AF, Myaskovsky L, Steel JL, DeVito Dabbs AJ. Posttransplant medical adherence: what have we learned and can we do better? *Curr Transplant Rep* 2018; **5**: 174.
- Sabaté E. *Adherence to Long-Term Therapies: Evidence for Action*. Geneva: World Health Organization, 2003.
- Dew MA, DiMartini AF, De Vito Dabbs A, *et al.* Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation* 2007; **83**: 858.
- Gokoel SRM, Gombert-Handoko KB, Zwart TC, van der Boog PJM, Moes D, de Fijter JW. Medication non-adherence after kidney transplantation: a critical appraisal and systematic review. *Transplant Rev* 2020; **34**: 100511.
- Nevins TE, Robiner WN, Thomas W. Predictive patterns of early medication adherence in renal transplantation. *Transplantation* 2014; **98**: 878.
- Low JK, Williams A, Manias E, Crawford K. Interventions to improve medication adherence in adult kidney transplant recipients: a systematic review. *Nephrol Dial Transplant* 2015; **30**: 752.
- Doesch A, Akyol C, Erbel C, *et al.* Increased adherence eight months after switch from twice daily calcineurin inhibitor based treatment to once daily modified released tacrolimus in heart transplantation. *Drug Des Devel Ther* 2013; **7**: 1253.
- Kuypers DRJ, Peeters PC, Sennesael JJ, *et al.* Improved adherence to tacrolimus once-daily formulation in renal recipients: a randomized controlled trial using electronic monitoring. *Transplantation* 2013; **95**: 333.
- Cassuto E, Pageaux GP, Cantarovich D, *et al.* Adherence to and acceptance of once-daily tacrolimus after kidney and liver transplant: results from OSIRIS, a French observational study. *Transplantation* 2016; **100**: 2099.
- Eberlin M, Otto G, Krämer I. Increased medication compliance of liver transplant patients switched from a twice-daily to a once-daily tacrolimus-based immunosuppressive regimen. *Transplant Proc* 2013; **45**: 2314.
- Fellström B, Holmdahl J, Sundvall N, Cockburn E, Kilany S, Wennberg L, editors. Adherence of renal transplant recipients to once-daily, prolonged-release and twice-daily, immediate-release tacrolimus-based regimens in a real-life setting in Sweden. *Transplant Proc* 2020; **52**: 3238.
- Taber DJ, Posadas-Salas A, Su Z, *et al.* Preliminary assessment of safety and adherence to a once-daily immunosuppression regimen in kidney transplantation: results of a randomized controlled pilot study. *Clin Transplant* 2020; **34**: e13844.
- Lai YL, Neo HLM, Vathsala A, Griva K. Comparing emotional adjustment of living-donor and deceased-donor kidney transplant patients. *Transplant Direct* 2020; **6**: e529.
- Dew MA, Rosenberger EM, Myaskovsky L, *et al.* Depression and anxiety as risk factors for morbidity and mortality after organ transplantation: a systematic review and meta-analysis. *Transplantation* 2015; **100**: 988.
- Nilsson M, Forsberg A, Bäckman L, Lennerling A, Persson LO. The perceived threat of the risk for graft rejection and health-related quality of life among organ transplant recipients. *J Clin Nurs* 2011; **20**: 274–282.
- Nilsson M, Persson LO, Forsberg A. Perceptions of experiences of graft rejection among organ transplant recipients striving to control the uncontrollable. *J Clin Nurs* 2008; **17**: 2408–2417.
- van Boekel GAJ, Kerkhofs CHH, Hilbrands LB. Treatment satisfaction in renal transplant patients taking tacrolimus once daily. *Clin Ther* 2013; **35**: 1821.
- Cleemput I, Dobbels F. Measuring patient-reported outcomes in solid organ transplant recipients. *Pharmacoeconomics* 2007; **25**: 269.
- Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther* 1999; **21**: 1074.
- Centraal Bureau voor de Statistiek. Educational level: Centraal Bureau voor de Statistiek 2020 [updated 2020]. Available from: <https://www.cbs.nl/en-gb/news/2017/26/older-generation-catching-up-on-social-media/education-level><https://www.cbs.nl/en-gb/news/2017/26/older-generation-catching-up-on-social-media/education-level>.
- Ichimaru N, Kakuta Y, Abe T, *et al.*, editors. Treatment adherence in renal transplant recipients: a questionnaire survey on immunosuppressants. *Transplant Proc* 2008; **40**: 1362.
- Sforza D, Iaria G, Petagna L, *et al.* Switch from twice-daily tacrolimus to once-daily, prolonged-release tacrolimus in kidney transplantation: long-term outcome. *Transplant Proc* 2019; **51**: 140.
- Kripalani S, Henderson LE, Chiu EY, Robertson R, Kolm P, Jacobson TA. Predictors of medication self-management skill in a low-literacy population. *J Gen Intern Med* 2006; **21**: 852.
- Maasdam L, Timman R, Cadogan M, *et al.* Exploring health literacy and self-management after kidney transplantation: a prospective cohort study. *Patient Educ Couns* 2021.