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ORIGINAL ARTICLE

Clinical consequences of non adherence to immunosuppressive medication in kidney transplant patients

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Summary

Little is known of the long-term clinical effects of non adherence on transplanted kidneys, especially regarding newer immunosuppressive regimens. In a study of 356 adult Swiss kidney transplant patients, non adherence was measured at inclusion by means of self-reporting, electronic monitoring, collateral reporting and blood assay. Long-term clinical outcomes regarding graft loss and creatinine levels were collected prospectively over a period of 5 years. A Cox proportional hazards model and mixed regression analysis were used, respectively, to examine the effects of non adherence on kidney survival and kidney function. The majority of patients (62%) were on immunosuppressive regimens that included mycophenolate mofetil, tacrolimus or sirolimus. No associations were found between non adherence and kidney graft survival or graft function. Notwithstanding weaknesses of this study, this negative result suggests that high adherence may protect patients against detrimental clinical outcomes, and/or that immunosuppressive regimens containing newer drugs allow wider non adherence margins than those based on previous generation medications such as cyclosporine, azathioprine and corticosteroids.

In recent decades, improvements in immunosuppressive medication have considerably increased the short-term life expectancy of transplanted kidneys by reducing the incidence of acute rejections, primarily in the first year post-transplant. However, over the same period, long-term patient survival curves have been relatively flat [1,2]. Extending the perspectives of kidney transplant recipients is therefore a profound challenge and an important research priority [3–5].

A major limiter of long-term survival is the gradual deterioration of kidney graft function [3–6], resulting from a range of function-impairing problems known collectively as chronic kidney dysfunction. Among the possible cause of chronic kidney dysfunction are behavioural aspects of the medication regimen, such as non adherence to the immunosuppressive prescription [5,7,8]. Next to the observation that non adherence has been linked to increased serum creatinine levels, a marker of decreased kidney function [9], the microscopic morphology of transplanted kidney tissue in non adherent patients shows a greater number of histological lesions than in those who adhere closely [10]. As surveys have shown that at least 28% of kidney transplant patients are non adherent to their regimens, non adherence may be a significant contributor to long-term kidney dysfunction [11].

One common disadvantage of existing studies exploring the associations between non adherence and clinical outcomes is that they were based predominantly on the older azathioprine- and cyclosporine-based regimens, which are no longer considered state-of-the-art. How far their conclusions can be applied to regimens using subsequent generations of medications, such as tacrolimus, mycophenolate mofetil or sirolimus is an issue that has previously only been investigated in a retrospective study of

Takemoto *et al.* [12]. New treatments are linked to a reduced incidence of acute rejection [13], and - as Takemoto *et al.* showed, also to graft loss [12]. However, because of their lower nephrotoxicity, it may be assumed that newer drugs are more tolerant of non adherence and that higher levels of non adherence are necessary to show long-term effects. Prospective studies are therefore needed to investigate the long-term effects of non adherence to current immunosuppressive regimens. The goal of this study was to prospectively explore the associations of non adherence with clinical outcomes, in a sample of stable transplant patients (>1 year transplanted), over a 5-year follow-up period, in a patient population that were on both earlier generation and newer regimens. Clinical outcomes were defined as kidney survival and kidney functionality (as reflected by serum creatinine levels).

Methodology

Design and sample

In 2001, we initiated the Supporting Medication Adherence in Renal Transplantation (SMART) study [14], a study aimed at investigating the prevalence, risk factors and clinical consequences of non adherence to immunosuppressive drugs in kidney transplant patients [15]. Our convenience sample included adult kidney transplant recipients (18 years of age or older), all of whom were at least 1 year post-transplant, managed their immunosuppressive intake independently, spoke and were acceptably literate in German or French, and made their yearly visits to one of the two included Swiss outpatient transplant clinics. Exclusion criteria were lack of the mental acuity necessary to answer the questions or an inability to read either French or German. Clinical outcome of these patients was collected prospectively over a period of 5 years. Complete information on the parent study can be found elsewhere [15,16].

Variables and measurement

Outcome variables

Clinical consequences of non adherence were assessed based on collected graft loss data and serum creatinine levels, which were systematically measured each time a patient visited the outpatient clinic. Creatinine data were collected for each patient from the time of enrolment in the study (between June 2001 and October 2002) until February 2007. Data on graft losses (all causes) were collected until March 2007. We measured our predictor variable, non adherence, using four methods: electronic monitoring (EM), self-reports, blood assay, and reports by health care workers.

Electronic monitoring of non adherence (EM)

A 3 month assessment of non adherence to immunosuppressive medication was performed using the MEMS®-V TrackCap system (Aardex Ltd., Zug, Switzerland). In clinically stable patients, EM is the most sensitive and valid measurement method for assessing non adherence, detecting even minor deviations from the prescribed treatment regimen [17]. The monitoring focussed on one immunosuppressive drug per patient, preferably the one taken twice daily (tacrolimus, mycophenolate mofetil, or cyclosporine). For the small number of patients still using a combination of azathioprine and prednisone, both drugs were monitored, as each of these drugs typically require one daily intake. We used the EM data to calculate (1) *the timing adherence* (the percentage of inter-dose intervals within 25% of the prescribed interval); and (2) the number of *drug holidays* per 100 monitored days, i.e., periods during which one or more consecutive dosages were missed [18]. For more details on EM measurement of non adherence in this study, we refer to a recent EM validation study [19].

Self-reported non adherence

Non adherence was also assessed by self-report, using one item of the Siegel scale [20]. On a 5-point Likert-type scale ranging from 'never forgot' (score 0) to 'forgot every day' (score 5), patients indicated how often over the past 4 weeks they had not taken their immunosuppressive drugs. As no validity, reliability or diagnostic values were reported for the scale by its developers, our research group assessed the diagnostic value of the four-item scale for the SMART study using electronic monitoring as a gold standard [21]. Non adherence was defined as any deviation from perfect adherence on any of the four items. Diagnostic values were: sensitivity, 23.3%; specificity, 89.8%; and likelihood ratio of a positive test result, 2.28 [21,22]. Predictably, these results indicate consistent underreporting – a common characteristic of self-reported non adherence measurement.

Blood assay

Adherence of patients taking cyclosporine, mycophenolate mofetil, tacrolimus, or sirolimus was also measured via drug trough medication levels at inclusion in the study. Based on the hospital's clinical guidelines, accepting a therapeutic range of 100–150 ng/ml for cyclosporine-A, 2–4 ng/ml for mycophenolate mofetil, and 5–10 ng/ml for sirolimus and tacrolimus, we categorized them into two groups: adherent (i.e. those within the range) and non adherent (i.e. patients outside the accepted values). The cut-off values were adapted if the patient's medical file indicated individualized target trough blood levels.

Collateral reporting by a nurse or physician

As a final, qualitative method of measuring adherence, in the weeks following inclusion, we asked various clinicians (seven physicians, four nurses and two medical assistants) involved in the participants' follow-up care to rate the adherence levels of those patients they were familiar with as good, fair, or poor. We then used the following algorithm to reduce the clinicians' scores for each patient into one ordinal variable from 0 (adherent) to 5 (non adherent). If all clinicians estimated adherence as good, the patient received a score of 0; patients who received at least one rating of fair, but none as poor, received scores of 1–4, according to the number of fair ratings. However, if even one clinician rated a patient's adherence as poor, the patient received a score of 5, regardless of the other clinicians' ratings [21].

Statistical analysis

To test whether creatinine levels were related to non adherence, we used linear mixed-effects modelling [23], in which we entered the 'patient' variable as a random intercept, and time, non adherence and the interaction of the two as fixed effects. The interaction term indicated whether the trajectory of creatinine differed for different levels of adherence. Testing of graft survival time was done using time-dependent Cox proportional hazards modelling [24]. Models were fit for each of the non adherence operationalizations described earlier. All analyses were performed using SAS release 9.1.

Results

Research team members approached 413 adult renal transplant recipients, during their yearly outpatient clinic check-up visits, regarding participation in the study. Of these, 86% agreed (N = 356). These patients were, on average, 6 years post-transplant. In all, 221 (62%) were on immunosuppressive regimens that included mycophenolate mofetil, tacrolimus or sirolimus. The sub sample for whom EM data was collected consisted of 249 patients,

Table 1. Demographic and clinical characteristics of the sample (n = 356).

Variable	Categories	Value
		Mean (SD)
Age in years		52.9 (13.5)
Length of time post-transplant in years		5.8 (6.4)
Number of HLA mismatches		4.3 (1.7)
		Frequency (%)
Gender	Male	207 (58.2%)
Living alone	No	273 (76.7%)
Employed	Yes	187 (52.6%)
Education	until age 11/12 years	50 (14.1%)
	until age 12/13–14/15 years	170 (47.9%)
	until age 15/16–18/19 years	36 (10.1%)
	advanced (college)	99 (27.9%)
Nationality	Swiss	291 (81.7%)
Currently smoking	No	280 (78.7%)
Panel reactive antibodies	0%	65 (87.7%)
	Higher (4–86%)	10 (12.3%)
Immunosuppressive regimens	Cyclosporine + mycophenolate mofetil	98 (27.6%)
	Cyclosporine + azathioprine	54 (15.2%)
	Cyclosporine	48 (13.5%)
	Azathioprine + Prednisone	25 (7.0%)
	Tacrolimus + azathioprine	23 (6.5%)
	Cyclosporine + mycophenolate mofetil + prednisone	18 (5.1%)
	Mycophenolate mofetil + prednisone	16 (4.5%)
	Tacrolimus + mycophenolate mofetil	13 (3.6%)
	Tacrolimus	12 (3.4%)
	Mycophenolate mofetil + sirolimus	8 (2.3%)
	Mycophenolate mofetil + sirolimus + prednisone	8 (2.3%)
	Tacrolimus + mycophenolate mofetil + prednisone	6 (1.7%)
	Other	36 (7.3%)

Table 2. Results of survival analyses: time until graft loss.

Variable	DF	Parameter estimate	Standard error	Chi-square	*P*-value	Hazard ratio
Blood assay	1	0.86645	0.57949	2.2356	0.1349	2.378
Collateral report	1	−0.76910	0.51186	2.2576	0.1330	0.463
Self-report	1	−0.99906	0.89895	1.2351	0.2664	0.368
Electronic monitoring: timing	1	−0.01439	0.01390	1.0713	0.3007	0.986
Electronic monitoring: drug holidays	1	0.09570	0.06436	2.2109	0.1370	1.100

This table shows Cox regression analysis estimates of the non adherence variables predicting graft loss. The hazard ratio column indicates the relative change in the probability of graft loss for each one-unit increase in the predictor variable. None of the predictive variables has a hazard ratio that is significantly different from one (i.e., higher values on the predictive variables are not associated with changes in the probability of graft loss).

Table 3. Results of random-effects models of serum creatinine over time.

Effect	F value	Pr > F
Blood assay	2.14	0.14
Collateral report	0.07	0.78
Self-report	0.04	0.83
Electronic monitoring: timing	0.28	0.59
Electronic monitoring: drug holidays	1.29	0.25

Each row of this table represents a random-effects model testing whether long-term changes in creatinine levels depended on the baseline adherence level. There is no evidence of a relationship.

and was very similar in composition to the full sample described in Table 1 [15]. Over the course of the study, of the total sample ($N = 356$), 81 subjects experienced graft loss (22.8%), of whom 33 (9.3%) returned to dialysis and 48 (13.5%) died (all causes).

Table 2 shows the results of the survival analyses, which used time to graft loss as the outcome variable and the various non adherence measures as predictors. We detected no relationship between graft loss and non adherence. Also, as shown in Table 3, creatinine levels for patients who showed higher non adherence at the start of the study did not evolve differently from those of their adherent counterparts.

Discussion

This cohort study tested whether, in patients more than 1 year post-transplant at enrolment, a relationship could be detected between non adherence and subsequent changes in kidney functionality, as indicated by graft survival and serum creatinine levels, over a period of more than 5 years. Unlike many previous studies, we did not measure acute rejections [9,25,26]. Because of the lack of a systematic biopsy protocol at the time of data collection, it is unknown whether more biopsies were taken in patients with graft problems; therefore, it is possible that the probability of detecting acute rejections was related to non adherence. Because non adherence is a possible cause of rejections, this may have introduced bias [10].

Although this study used a larger sample, more varied and more sensitive measurement methods than those previously published [9,10], our analyses did not indicate any relationship between graft survival/creatinine levels and non adherence to the immunosuppressive regimen. This absence of any positive result is significant, because it could mean that the newer, less nephrotoxic medications used reduced the detrimental effect of non adherence. Indeed, there are indications that abandonment of nephrotoxic immunosuppressants could lead to improved long-term kidney transplantation outcomes [27,28]. However, whether adherence is a mediating factor in this relationship needs to be investigated. Thus, before concluding that the newer immunosuppressive regimens offer benefits superior to their predecessors, a number of issues specific to this study have to be taken into account.

Previous work by our group indicates that the adherence level of this study's sample was exceptionally high: the mean percentage of prescribed immunosuppressive doses taken was 98.4 [29,30]. This may explain why our results are different from those of Takemoto *et al.* [12], who found a relationship between non adherence and poor outcomes in a mycophenolate mofetil-based regimen. Although that study used a different measurement method (pharmacy refills), their reported mean taking adherence percentage of 81% suggests considerably higher non adherence in their sample. The difference in findings of Takemoto *et al.* and our study may indicate that, if the sample's overall adherence level exceeds a certain threshold, the effect of non adherence may drop.

It is also noteworthy that, in our study, adherence-enhancing interventions were carried out in non adherent patients immediately following the baseline measurement [16]. Although the results of that intervention showed a waning effect after 9 months, the possibility of a slight

permanent enhancement of adherence, even after 5 years, cannot be fully excluded.

There were also indications that our sample was relatively unsusceptible to chronic kidney dysfunction because of low average panel reactive antibody levels and the large number of patients on monotherapy. One-sixth of participants ($n = 62$) were on monotherapy, indicating that their condition was well-controlled. Further, we did not start with a cohort of freshly transplanted patients: non adherent patients most susceptible to poor outcomes might already have been lost in early post-transplant phases, i.e. before they could enrol in this study. This limitation is a consequence of the fact that, although we collected clinical outcome data prospectively, the parent study combined prospective with retrospective data collection methods.

Issues of measurement and missing data could also have reduced the ability of our study to detect associations. Primarily, this is because, although non adherence is a behaviour that can change over time, we measured it only once, thereby missing any adherent periods that may have occurred after baseline measurement. Second, because graft loss-related drop-out of non adherent patients may have obscured increased creatinine levels, we may have failed to detect a relationship between them and non adherence.

With this study, we were unable to replicate earlier findings linking non adherence to diminished graft function or graft loss. Comprehensive prospective studies such as the ongoing Swiss Transplant Cohort Study may reveal more robust insights regarding the relationship between adherence and long-term graft function in this population, and clarify whether our sample's high level of adherence was indeed the main factor in reducing the risk of poor outcomes and/or whether the use of newer immunosuppressants changed the thresholds at which non adherence is harmful.

Authorship

SDG, JS, AB: conception of the study. KD: writing of the article. KD: analysis of the data. FB, PSK: operationalization of the variables. SDG, FB, PSK, JS, AB: review of the manuscript.

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References

1. Meier-Kriesche HU, Schold JD, Kaplan B. Long-term renal allograft survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? *Am J Transplant* 2004; **4**: 1289.
2. Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. *Am J Transplant* 2004; **4**: 378.
3. Pascual M, Theruvath T, Kawai T, Tolkoff-Rubin N, Cosimi AB. Strategies to improve long-term outcomes after renal transplantation. *N Engl J Med* 2002; **346**: 580.
4. Nolan CR. Strategies for improving long-term survival in patients with ESRD. *J Am Soc Nephrol* 2005; **16**(Suppl. 2): S120.
5. Habwe VQ. Posttransplantation quality of life: more than graft function. *Am J Kidney Dis* 2006; **47**: S98.
6. Yang H. Maintenance immunosuppression regimens: conversion, minimization, withdrawal, and avoidance. *Am J Kidney Dis* 2006; **47**: S37.
7. Adams PL. Long-term patient survival: strategies to improve overall health. *Am J Kidney Dis* 2006; **47**: S65.
8. Howard AD. Long-term posttransplantation care: the expanding role of community nephrologists. *Am J Kidney Dis* 2006; **47**: S111.
9. Vlaminck H, Maes B, Evers G, *et al.* Prospective study on late consequences of subclinical non-compliance with immunosuppressive therapy in renal transplant patients. *Am J Transplant* 2004; **4**: 1509.
10. Lerut E, Kuypers DR, Verbeken E, *et al.* Acute rejection in non-compliant renal allograft recipients: a distinct morphology. *Clin Transplant* 2007; **21**: 344.
11. Denhaerynck K, Dobbels F, Cleemput I, *et al.* Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. *Transpl Int* 2005; **18**: 1121.
12. Takemoto SK, Pinsky BW, Schnitzler MA, *et al.* A retrospective analysis of immunosuppression compliance, dose reduction and discontinuation in kidney transplant recipients. *Am J Transplant* 2007; **7**: 2704.
13. Brennan DC. Long-term trends in allograft survival. *Adv Chronic Kidney Dis* 2006; **13**: 11.
14. De Geest S, Denhaerynck K, Schafer-Keller P, Bock A, Steiger J. Supporting medication adherence in renal transplantation–the SMART study. *Swiss Med Wkly* 2007; **137**(Suppl. 155): 125S.
15. Denhaerynck K, Steiger J, Bock A, *et al.* Prevalence and risk factors of non-adherence with immunosuppressive medication in kidney transplant patients. *Am J Transplant* 2007; **7**: 108.
16. De Geest S, Schafer-Keller P, Denhaerynck K, *et al.* Supporting medication adherence in renal transplantation (SMART): a pilot RCT to improve adherence to immunosuppressive regimens. *Clin Transplant* 2006; **20**: 359.
17. Liu H, Golin CE, Miller LG, *et al.* A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med* 2001; **134**: 968.

18. Vrijens B, Goetghebeur E. Comparing compliance patterns between randomized treatments. *Control Clin Trials* 1997; **18**: 187.
19. Denhaerynck K, Schafer-Keller P, Young J, Steiger J, Bock A, De Geest S. Examining assumptions regarding valid electronic monitoring of medication therapy: development of a validation framework and its application on a European sample of kidney transplant patients. *BMC Med Res Methodol* 2008; **8**: 5.
20. Siegal B, Greenstein SM. Differences between compliers and partial compliers: a multicenter study. *Transplant Proc* 1998; **30**: 1310.
21. Schafer-Keller P, Steiger J, Bock A, Denhaerynck K, De Geest S. Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. *Am J Transplant* 2008; **8**: 616.
22. Schäfer-Keller P, Steiger J, Denhaerynck K, Bock A, De Geest S. Using electronic monitoring as reference standard: how well do state of measurement methods measure medication adherence in kidney transplant recipients? *Am J Transplant* 2005; **5**: 331.
23. Verbeke G, Molenberghs G. *Linear Mixed Models for Longitudinal Data*. New York: Springer, 2000: 568 pp.
24. Allison PD. *Survival analysis using the SAS system: a practical guide*. Cary, NC: SAS Institute Press, 1995: 292 pp.
25. De Geest S, Abraham I, Moons P, *et al.* Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. *J Heart Lung Transplant* 1998; **17**: 854.
26. Hilbrands LB, Hoitsma AJ, Koene RA. Medication compliance after renal transplantation. *Transplantation* 1995; **60**: 914.
27. Guerra G, Srinivas TR, Meier-Kriesche HU. Calcineurin inhibitor-free immunosuppression in kidney transplantation. *Transpl Int* 2007; **20**: 813.
28. Ponticelli C. Can mTOR inhibitors reduce the risk of late kidney allograft failure? *Transpl Int* 2008; **21**: 2.
29. Denhaerynck K, Dobbels F, Desmyttere A, De Geest S. Differences in health beliefs regarding immunosuppressive medication between European and American kidney transplant recipients. *Am J Transplant* 2006; **6**: S494.
30. Denhaerynck K, Manhaeve D, Dobbels F, Garzoni D, Nolte C, De Geest S. Prevalence and Consequences of Nonadherence to Hemodialysis Regimens. *Am J Crit Care* 2007; **16**: 222.

