



## Physician reported adherence to immunosuppressants in renal transplant patients: Prevalence, agreement, and correlates



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### ABSTRACT

**Objective:** Adherence to immunosuppressants (IS) is crucial to prevent allograft rejection. Even though there is evidence that non-adherence to IS among kidney transplant recipients is common, it is rarely routinely assessed in clinical practice. Especially, little is known about how physicians estimate patients' adherence to IS medication. **Methods:** In a single center, cross-sectional study adult patients at least 1 year after kidney transplantation were asked to complete measures of adherence (BAASIS®, Transplant Effect Questionnaire) and of general psychopathology (anxiety, depression, perceived social support). Also the physicians were asked to estimate their patients' adherence. Medical data (time since transplantation, treatment for rejection, IS serum trough levels and target levels) were taken from the patients' charts.

**Results:** Physicians rated 22 of 238 (9.2%) patients as non-adherent. Physicians' estimations of non-adherence were lower compared to the results of the self-ratings and biopsy-proven rejections. No association was found between physicians' estimates and the variability of IS through levels. Significantly more women and patients who reported that their native language was not German were rated as non-adherent by the physicians. Also, physician-rated non-adherent patients reported significantly higher depression and anxiety scores as well as less social support compared to adherent patients.

**Conclusion:** Our results suggest that physicians tend to underestimate patient non-adherence to IS medication. They appear to use observable cues such as sex, language skills, and elevated anxiety and depression scores in particular, to make inferences about an individual patient's adherence. Underestimation of medication non-adherence may impede physicians' ability to provide high quality care.

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### Introduction

Even though adherence to immunosuppressants (IS) is crucial to prevent acute cellular allograft rejection as well as (late) antibody mediated rejection a substantial proportion of transplant recipients are non-adherent to their IS regimen. Regular and adequate dosing is required to achieve therapeutic outcomes by IS therapy. Already minor deviations from the dosing schedule suffice to increase the risk of future graft loss and death [1,2,3,4]. Non-adherence can occur early after transplantation and has been shown to increase over time [5,6]. Among renal transplant patients on average 35.6% of patients per year have been reported to be non-adherent to IS medication [7], although estimates range from 2% to 67% [8]. In a recent study 47% of all kidney transplant recipients with rejection losses had been independently identified in the past (as assessed with chart reviews) as non-adherent by attending clinicians [9]. Several authors have suggested that poor adherence to IS

treatment is still the leading preventable cause of graft loss [10,11]. Graft failure not only results in (re)initiation of dialysis and the associated reduction in quality of life, it is also associated with increased health care costs [12]. In addition, expected survival is significantly lower when patients return to dialysis, and re-transplantation of the patient might be hampered by new HLA-antibodies.

There are several direct and indirect adherence measuring instruments available, nevertheless addressing adherence to medication is notoriously difficult [13] and is rarely routinely done prospectively and continuously in a standardized manner in clinical practice. Existing measures such as pill counts, drug levels, allograft rejection, physicians' estimation and patient self-reports have strengths and weaknesses [1,13,14]. Electronic monitoring systems which have been considered to come closest to a gold standard in measuring adherence are costly and impractical for routine clinical monitoring.

Little is known about how attending physicians estimate their renal transplant patients' adherence to IS medication. In busy clinical practices, physicians must often make estimates of their patients' adherence without any external aids [15]. In addition, physicians are frequently reluctant to directly discuss the issue of adherence with their patients

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as has been suggested by Curtis et al. [16]. This might be due to lack of time, lack of communication skills, and uncertainty about or unavailability of helpful strategies to improve adherence. However, if physicians are unaware of non-adherence they are unable to address it. Not detected non-adherence may lead to the failure to identify patients in need for an intervention and thus to the withholding or unnecessary delay of treatment [17,18,19].

Prior studies suggest that physicians tend to estimate their patients' adherence inaccurately usually underestimating medication non-adherence [20,21,22,23]. In addition, physicians' reports have been found to have the lowest sensitivity to non-adherence with IS when using electronic monitoring as the reference standard [10]. However, there is only scarce literature on how physicians' estimate of non-adherence with IS agrees with other adherence measures. In addition, no study has specifically examined the associations of physicians' adherence estimates with other putative correlates of adherence (e.g. depression) or has investigated medical and patient factors that might influence physicians' judgment. For instance there is strong evidence from other medical fields that there is a physician bias with regard to gender, usually to women's disadvantage. This has been understudied in the previous transplant literature.

Thus we aimed at investigating:

- 1) the prevalence of non-adherence with IS as estimated by the transplant physician;
- 2) the correlation between the physicians' estimate and other adherence measures, i.e. patients' self-report, IS serum trough level variability, and biopsy-proven rejection;
- 3) the difference between adherent and non-adherent patients according to the physicians' estimation with regard to socio-demographic variables, medical data (i.e. type of IS, time since transplantation, BMI, prior dialysis, duration of dialysis, number of transplants), and psychological patient factors (depression, anxiety, perceived social support).

## Methods

### Procedure and data collection

We conducted a single-center, cross-sectional study of kidney transplant recipients who were at least 1 year post-transplant and had no non-renal allografts. Further inclusion criteria were age of at least 18 years and an intake of immunosuppressant (IS) of the calcineurin-inhibition- and/or mTOR-inhibition-type. Exclusion criteria were insufficient German language skills and impaired cognitive status interfering with the understanding of the questionnaires. All patients attending the kidney transplant outpatient clinic of Hannover Medical School for a follow-up visit from November 2014 to February 2015 were screened and 311 patients met the aforementioned inclusion criteria. The Ethics Committee of the Hannover Medical School approved the study and all patients gave their written informed consent.

All patients completed the self-report instruments (questionnaires) while they were waiting to see the transplant physician for their follow-up visit. A doctoral student (S.P.) not belonging to the transplant team approached each patient who met the inclusion criteria during their regular yearly check-up visits to the outpatient clinic. Patients were informed that the physician would be blind to the results of their self-ratings.

### Adherence assessments

#### Physician's adherence estimation

The physicians were asked to estimate each patient's current IS drug adherence on a scale ranging from 1 = very good adherence to 5 = very poor adherence. If the physician categorized the patient's adherence as less than "good" the patient was classified as non-adherent. Similar

measurement methods for physician reports have been employed by others [10,20]. Physicians were blind to the results of the adherence ratings reported by the patients themselves; however, they were aware of all medical data including IS serum levels and rejection episodes during the last 12 months. Fourteen physicians rated between 2 and 41 patients each. Six female physicians evaluated 115 patients and 8 male physicians 123 patients. None of the physicians who rated the patients was involved in study design, study conduct, or reporting.

#### Self-reported adherence

To estimate the self-reported IS drug adherence we used the 4-item Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS®) which is the recommended self-report instrument for measuring adherence to IS [1]. Participants were asked about how often, over the last 4 weeks, they (1) had not taken their drugs (taking dimension), (2) had taken their medication more than 2 h before or after their prescribed taking time (timing dimension), (3) had skipped at least two consecutive doses of their drugs (drug holidays), and/or (4) had reduced the prescribed amount of their medication (dose reduction). Responses were given on a 6-point scale ranging from 0 (never) to 5 (every day). Non-adherence was dichotomously defined as any self-reported non-adherence on any of the 4 items (response > 0). In addition we tabulated a total score for the four items resulting in a continuous adherence rating with scores ranging from 0 to 20 as suggested by De Bleser et al., [20].

#### Transplant Effect Questionnaire (TxEQ)

The adherence subscale of the German version of the Transplant Effect Questionnaire (TxEQ; [24]) was used. The adherence subscale consists of 5 items to be scored on a 5-point Likert scale ranging from 1 = "strongly agree" to 5 = "strongly disagree". The mean value of the items was computed. Lower values correspond with lower self-reported adherence. The internal consistency of the adherence subscale in our sample was moderate but satisfactory with  $\alpha = .769$ .

#### Assessment of rejection episodes

The patient charts were controlled for any type of biopsy-proven rejection episodes followed by a rejection treatment within the previous 12 months. Rejection episodes have been considered to be the outcome measure that is most closely related to non-adherence [14]. Although non-adherence is not the only possible reason for rejection, it certainly is a preventable cause for it.

#### Blood-assays (serum trough level variability)

Measuring serum medication levels is a standard practice to monitor adequacy of IS in the outpatient setting. Variability of trough levels of cyclosporine A, tacrolimus, or mTOR inhibitors (sirolimus or everolimus) including all trough levels over a period of 12 months was calculated as a potential objective tool to monitor medication non-adherence. In our outpatient clinic we measure trough levels instead of 2 h post-dose levels for cyclosporine A, as well. Only validated trough levels were included; levels that were apparently measured after IS intake were excluded. The IS serum level variability was analyzed by calculating the intra-patient coefficient of variation (CV) for each patient based on the target serum concentration. We used the following algorithm: for the standardization of the values each patient's trough levels were divided by the respective individual target levels. Means and standard deviations (SD) were computed for these standardized trough levels and CV was calculated by dividing the SDs by the means as suggested by Hsiao et al. [25]. A minimum of 4 trough levels was required to calculate the CV which was available in 218 patients. A higher CV is indicative of more erratic levels without skewing to those individuals with higher mean IS levels, and thus eliminating the confounding effects that the use of just the SD presents. CV showed a more pronounced difference between patients with rejection versus without rejection than SD [25].

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