



# Awareness of Memory Impairment Increases the Adherence to Immunosuppressants in Kidney Transplant Recipients

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## ABSTRACT

**Objectives.** Nonadherence to immunosuppressive drugs is a concern among kidney transplantation recipients (KTRs). The adverse effects of immunosuppressive drugs can trigger nonadherence and lead to a great impact on the allograft survival. The aim of this prospective controlled study is to determine the major adverse effects of immunosuppressive drugs and their correlation with the nonadherence in kidney transplantation recipients.

**Methods.** All data were collected from medical and pharmacy records. We use modified Immunosuppressant Therapy Adherence Scale combined with Modified Transplant Symptom Occurrence and Symptom Distress scale to explore the relationship between symptom experience related to side effects of immunosuppressants and adherence. The risk of nonadherence was estimated by stepwise logistic regression while controlling for age, gender, education, and immunosuppressive medications. Multivariable analysis was performed using a single random effect of  $P < .2$ .

**Results.** In total, 412 KTRs completed the structured self-report instrument. The weekly pill counts were  $84.2 \pm 39.8$ . Overall, 21.4% of patients were nonadherent to immunosuppressive drugs. The most common adverse effects of immunosuppressive drugs were memory impairment (28.4%), insomnia (26.0%), gastrointestinal discomfort (21.4%), easy fatigue (22.1%), hand tremor (23.8%), and vision variation (29.1%). Multivariate analysis revealed that the adherence increased in patients with awareness of memory impairment (odds ratio 2.320, 95% confidence interval: 1.259–4.274,  $P = .007$ ). There was no significant difference in the incidence of acute rejection, gender, age, and education between adherent and nonadherent patients.

**Conclusion.** In summary, these results indicate a significant prevalence of nonadherence to immunosuppressive drugs in kidney transplantation recipients. Awareness of memory impairment significantly affected adherence to immunosuppressive drugs.

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**A**LTHOUGH there has been a marked improvement of immunosuppressive therapy in the past decade, nonadherence to immunosuppressive drugs remains one of the most important causes of renal allograft loss in kidney transplant recipients. Many adverse effects of immunosuppressive drugs may trigger the nonadherence of kidney transplant recipients and lead to a great impact on allograft survival. This prospective controlled study aims to determine the major adverse effects of immunosuppressive drugs and their correlation with nonadherence in kidney transplant recipients. This study also assesses the rates of nonadherence to immunosuppressive therapy and evaluates the impact factors and their correlation with nonadherence in kidney transplant recipients.

## METHODS

A cross-sectional questionnaire survey was used in this study. The study protocol has been approved by the Ethics Committee of Taichung Veterans General Hospital (Taichung, Taiwan; IRB

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number: C10003). Between September 2010 and December 2010, the kidney transplant recipients who regularly visited the transplantation outpatient clinic of Taichung Veterans General Hospital were recruited. All of the participants signed the informed consent statement and were asked to complete an anonymous questionnaire, which included questions of patient demographics (age, gender, and education), characteristics related to kidney transplantation, usage of immunosuppressive drugs, and major side effects of immunosuppressive drugs or complications after kidney transplantation. The survey used in this study was modified from the Immunosuppressant Therapy Adherence Scale (ITAS)<sup>1</sup> combined with the Modified Transplant Symptom Occurrence and Symptom Distress (MTSOSD) scale.<sup>2</sup> We use this survey to explore the relationship between symptom experience related to side effects of immunosuppressants and adherence.

The ITAS used the four-item instrument. Patients were asked how often during the past week they: (1) forgot to take their medications (including immunosuppressants); (2) stopped taking medications because they felt better; (3) stopped taking medications because they felt worse; and (4) missed taking medications for any reason. The response options for each item were coded: 3 = “0% of the time (none),” 2 = “1% to 20% of the time,” 1 = “21% to 50% of the time,” and 0 = “greater than 50% of the time.” Summing up response codes allowed us to assign scores. The scoring was from 0 to 12.<sup>1</sup>

Nonadherence may be triggered by adverse events or difficulties taking medications. The MTSOSD scale was modified as a self-reporting 50-item instrument constructed of possible adverse effects of immunosuppressive drugs or complications after kidney transplantation. Patients were asked if they experienced difficulty when: (1) clearly reading medication directions; (2) remembering the time and number of tablets to take; (3) using pillbox or not.

All statistical analyses were performed using the Statistical Program of Social Sciences (SPSS version 17.0 for Windows, SPSS Inc, Chicago, IL). Statistical significance was defined as a *P* value less than .05. The risk of nonadherence and side effects was estimated by stepwise logistic regression while controlling for age, gender, education, and immunosuppressive medications. Multivariable analysis was performed using a single random effect of *P* < .2.

**RESULTS**

A total of 412 stable kidney transplantation recipients (218 men and 194 women) were interviewed and completed the modified ITAS and MTSOSD scale. The mean age was 51.5 ± 12.0 years (range, 18 years to 85 years). The mean duration after kidney transplantation was 8.1 ± 5.8 years (range, 0.1 years to 24.2 years). Of them, 368 patients (89%) were from cadaveric sources. The mean level of serum creatinine was 1.5 ± 0.6 mg/dL (range 0.6 mg/dL to 4.8 mg/dL). The immunosuppressive drugs used included prednisolone (74.3%), cyclosporine (21.6%), prograf (32%), advagraf (35.2%), cellcept (45.9%), myfortic (29.1%), and sirolimus (18.9%). The immunosuppressive regimens used were advagraf-based (33.3%), tacrolimus-based (32%), cyclosporine-based (21.4%), and sirolimus-based (12.4%). Twenty-one (5.1%) patients had an episode of acute rejection within 1 year before the study.

The percentages of educational levels of below junior high school, high school, and above college level were 36%, 35%, and 29%, respectively. The mean number of daily medications

taken was 5.9 ± 2.2 (range, 1 to 13). The mean number of daily frequencies for medications taken was 4.0 ± 1.7 (range, 1 to 11). The difficult situations noted with regard to taking medications included reading medication directions (6.8%), remembering to take medication on time (5.6%), and remembering the number of tablets to take (4.1%). A total of 43.4% of patients used a pillbox to assist with them while taking medications.

According to the modified ITAS scale, 68 (16.4%) had ever forgotten to take medications in the previous week and 87 (21.1%) had missed taking medications for any reason. However, very few (< 0.2%) patients stopped taking medications because they felt better or worse. Three hundred twenty-four patients (78.6%) were adherent to immunosuppressive drugs and the remaining 88 (21.4%) were nonadherent. The adverse effects and complications of immunosuppressive drugs after kidney transplantation (Table 1) were significantly correlated with the adherence to immunosuppressive drugs. The most common adverse effects of immunosuppressive drugs were neuromuscular-related (59.5%), central nervous system-

**Table 1. Major Adverse Effects Posttransplantation (N = 412)**

Adverse Effects	Events	%
Central nervous system-related	219	53.2
Awareness of memory problems	117	28.4
Sleep difficulties	107	26.0
Increased thirst	65	15.8
Restlessness/nervousness	59	14.3
Dizziness	57	13.8
Hearing loss	50	12.1
Headaches	45	10.9
Anxiety	42	10.2
Cardiovascular-related	69	16.7
Palpitations	60	14.6
Hormone-related	52	12.6
Gastrointestinal-related	208	50.5
Stomach complaints/nausea/vomiting	88	21.4
Excessive appetite	52	12.6
Diarrhea	50	12.1
Swollen gums	44	10.7
Sores on lips or in mouth	44	10.7
Neuromuscular-related	245	59.5
Difficulty seeing well	120	29.1
Trembling hands	98	23.8
Tiredness	92	22.3
Lack of energy	91	22.1
Joint pain	71	17.2
Muscle cramps	62	15.0
Lack of energy	53	12.9
Increased urge to urinate	45	10.9
Outlook-related	166	40.3
Thinning of hair/hair loss	101	24.5
Moon face	53	12.9
Dermatological-related	215	52.2
Bruises	90	21.8
Dry skin	60	14.6
Itching	52	12.6
Brittle fingernails	43	10.4

related (53.2%) and dermatology-related (52.2%). The most common adverse effects of immunosuppressive drugs were memory impairment (28.4%), insomnia (26.0%), gastrointestinal discomfort (21.4%), easy fatigue (22.1%), hand tremor (23.8%), and vision variation (29.1%). Multivariate analysis revealed that the adherence significantly increased in patients with awareness of memory impairment (odds ratio [OR] = 2.320, 95% confidence interval [CI] 1.259–4.274,  $P = .007$ ) and decreased with brittle fingernail (OR = 0.434, 95% CI: 0.207–0.909,  $P = .027$ ). Moreover, there was no significant difference in the number of rejections, gender, age, or education between adherent and nonadherent patients.

## DISCUSSION

The adherence of immunosuppressive drugs has a great impact on the survival of renal allografts. The adverse effects of immunosuppressive regimens could also affect the adherence in kidney transplant recipients. In this study, we reported an alarming percentage of adverse events among kidney transplant recipients. The most common three adverse effects of immunosuppressive drugs were present in more than half of the study subjects: neuromuscular-related (59.5%), central nervous system-related (53.2%), and dermatology-related (52.2%). In more detail, difficulty seeing well, awareness of memory impairment, and sleep difficulties were the most common adverse effects with incidences of 29.1%, 28.4%, and 26%, respectively.

The adverse effects of immunosuppressive agents after kidney transplantation were diverse. The presence of symptoms or complications may promote medication adherence. Otherwise, actual or perceived unpleasant adverse effects would reduce medication adherence.<sup>3,4</sup> Memory impairment could be strongly associated with nonadherence. In this study, we did not perform a complete survey for memory impairment. Thus, we have not provided enough

evidence for the correlation between memory impairment and nonadherence. However, the awareness of memory impairment strongly promotes patients to use a pillbox or ask for support from family members. This indicated that a more complete survey regarding memory impairment could be important in kidney transplant recipients.

Abdelaziz et al have reported a very high prevalence (56.6%) of onychomycosis-related fingernail problems in kidney transplant recipients.<sup>5</sup> Our results did not support this unique high prevalence. The prevalence of brittle fingernail in our study was only 10.4%. The reason for any brittle fingernail-related decrease in patient adherence to medication schedules remains unclear.

In conclusion, the awareness of memory impairment significantly affected patient adherence to immunosuppressive drug schedules in kidney transplantation recipients. The risk of nonadherence also increased for patients with brittle fingernails. Interventions to improve patient adherence should target patients who have brittle fingernails and the awareness of memory impairment.

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