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# Adherence to Immunosuppressants among Adult Patients after Allogeneic Hematopoietic Stem-Cell Transplantation (Allo-HSCT): A Cross-Sectional Study

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**ABSTRACT**

**Background:** The level of adherence to drug therapy after allogeneic hematopoietic stem-cell transplantation (Allo-HSCT) can affect the patient's outcome, and poor adherence is one of the factors in first-year mortality after HSCT.

**Material and Methods:** This study assessed adherence to cyclosporine and prednisolone as the immunosuppressant regimen in 110 post-HSCT patients (> 18 years). Demographic characteristics, clinical information, and cyclosporine levels were obtained. A validated Persian medication adherence scale was used to assess adherence to cyclosporine and prednisolone.

**Results:** For 110 patients, the calculated mean of the total score of cyclosporine and prednisolone was 7.73 ± 0.62 and 7.63 ± 0.73, respectively. Poor adherence to medication in this population was 27.7% and 22.7% to prednisolone and cyclosporine, respectively. A significant correlation was observed between adherence total score and cyclosporine levels at the third- and fourth-month post-transplant ($r = 0.52$, $P < 0.001$ and $r = 0.60$, $P = 0.001$). In the first, second, and third months, the mean of cyclosporine levels in the high adherence level was higher than the moderate and poor adherence levels. Additionally, there was an association between adherence score and the level of cyclosporine. One score increase in adherence scale on average increased cyclosporine level by 34.48 ng/ml.

**Conclusion:** In this study, medication non-adherence was high, which indicates the need for more careful monitoring of post-HSCT patients' medication use. This is even more crucial currently since it has been confirmed that adherence can affect cyclosporine levels as the most effective immunosuppressant agent in preventing graft-versus-host disease (GVHD).

**Keywords:** Medication adherence; Treatment adherence and compliance; Immunosuppressive agents; Transplantation; Homologous; Hematopoietic stem cell transplantation; Cyclosporine

## INTRODUCTION

Allogeneic hematopoietic stem-cell transplantation (Allo-HSCT) is known as an effective treatment for patients with malignant diseases. This treatment is used to cure numerous oncological, hematological, and immunological diseases [1-3]. Careful close monitoring after Allo-HSCT is critical for transplantation success. The most important step after Allo-HSCT, which necessitates follow-up, is the applied medication regimen to prevent graft-versus-host disease (GVHD) and infections.

Numerous medications are involved in this regimen, most notably immunosuppressants and corticosteroids[1-3]. The main immunosuppressant drug classes (and their most used drugs) that are given for preventing GVHD are steroids (methylprednisolone or prednisolone), antimetabolites (methotrexate), calcineurin inhibitors (cyclosporine or tacrolimus), mTOR kinase inhibitors (sirolimus), polyclonal antibody (anti-thymocyte globulin), monoclonal antibodies (alemtuzumab), and mycophenolate mofetil [4]. These drugs should be used accurately, with the right dose and at the right time, unless patients will face complications, such as infection, renal failure, and, most importantly, GVHD[2,3,5]. It is estimated that about 30-60% of post-HSCT patients develop GVHD[6]. Graft-versus-host disease can lead to increased morbidity and mortality, reduced quality of life[7,8], and consequently an increase in healthcare costs[9].

Graft-versus-host disease occurs after a patient's discharge from the hospital with several drugs that should be taken through a complex schedule. This schedule includes different doses, frequencies, and timing of all the drugs, which also might change in the future and would make it even harder for patients to take them properly[2,10]. This post-Allo-HSCT therapy might continue for months to years and is essential for better patient prognosis[1, 11].

The World Health Organization (WHO) has defined adherence as "the extent to which a person's behavior, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider"[12]. There are reviews that report generally poor adherence in different types of diseases[13,14]. Accordingly, 29% of drug-related hospitalizations are linked to non-adherence to medication [15]. In cancer patients, the rate of non-adherence to the drug is reported to be more than 20% [2]. However, the rate of poor medication adherence in the post-HSCT population has been reported to be more than 50% by Lehrer et al.[1] and Pai et al[16].

The level of adherence after Allo-HSCT can affect the patient's outcome[16]. Non-adherence to medication is one of the factors in the first-year mortality after HSCT[5]. The more complicated and prolonged medication therapy regimen[8,10] reduces patients' adherence. Due to the fact that post-HSCT medication therapy has both of these characteristics, the risk of non-adherence in these patients is potentially high[17].

Considering the high rate of poor adherence in bone marrow transplant (BMT) patients and the severity of its consequences, the quality of adherence in Allo-HSCT patients is not evaluated as much as required. The aim of this study was to assess the adherence to immunosuppressant medications that are used in post-Allo-HSCT adult patients in the current study's setting and related factors.

## Materials and Methods

### Study Design and Setting

This cross-sectional observational study assessed adherence to an immunosuppressant regimen in patients after Allo-HSCT. The present study was conducted within December 2014 and April 2016 in the post-BMT outpatient clinic of Shariati hospital, affiliated with Tehran University of Medical Sciences (TUMS), Tehran, Iran. The patients were discharged from the BMT ward with the GVHD prophylaxis regimen based on the hospitals' guidelines, which consists of only two immunosuppressant drugs: oral cyclosporine and oral prednisolone. In case of GVHD occurrence, the medication therapy regimen would have changed.

### Participants

A two-week study on 110 patients was performed in order to become familiar with the clinic, check the patient recruiting process, and evaluate data sheet appropriateness and validity. Additionally, the aforementioned two-week study was used to estimate the sample size. This study found a

standard deviation (SD) = 1.04 with d = 0.25 for cyclosporine and SD = 1.22 with d = 0.25 for prednisolone. The aforementioned values were used in the Cochran formula, and by considering a 20% loss, the sample size was calculated at 110 patients.

A total of 110 adult patients (>18 years) were recruited for the study, who underwent Allo-HSCT in the BMT center of Shariati hospital and received cyclosporine afterward. The patients were excluded if more than 6 months had passed from their transplantation or their immunosuppressant regimen had changed.

All the patients agreed to participate and signed a consent form before they participated in the study. The study was approved by the Institutional Ethics Committee of TUMS with the reference number 189363-p-5442.

**Data Collection**

One senior pharmacy student used a data collection sheet for gathering different patients' information and two adherence questionnaires for assessing the adherence to cyclosporine and prednisolone separately, and every patient was interviewed only once.

**Data Collection Sheet**

A checklist for collecting different measures from patients was designed. This checklist included the four following sections:

1. Demographic characteristics: Gender, age, marital status, education level, job, and contact information
2. Clinical information: Type of malignancy and time of its diagnosis, frequency of transplantation, last transplantation date, frequency of relapses, any underlying diseases, and donor gender/age/relationship with the recipient
3. Drug information: List of immunosuppressant drugs, list of prophylactic drugs for bacterial, viral, and fungal opportunistic infection, list of drugs for HSCT side effect management, and list of drugs related to patient's underlying disease (if any)
4. Cyclosporine information: Last dose of received cyclosporine, cyclosporine trough level (i.e., 12 hours after the last dose or immediately before the next dose), cyclosporine serum levels (in order to have cyclosporine serum concentration during one month, the average of all recorded concentrations had also been determined).

**Adherence Questionnaire**

The former validated Persian version of the eight-item Morisky Medication Adherence Scale (MMAS-8) [18, 19] was used to assess patients' adherence to their immunosuppressant regimen. Items M1 to M7 are "Yes or No" questions and item M8 is based on a Likert scale with a different scoring method. The score for the MMSA-8 was calculated for every patient. Choosing "No" as an answer in M1-M4, M6, and M7 and "Yes" in M5 are counted as positive scores. M8 scored differently as "Never/Rarely" with a 1 score, "Once in a while" with a 0.75 score, "Sometimes" with a 0.5 score, "Often" with a 0.25 score, and "Always" with a 0 score. These scores all are summed up at the end, and scores lower than 6, 6-7.75, and 8 show low, moderate, and high adherence, respectively. At the end, the mean (SD) of the total score was obtained. This scale was completed by face-to-face interviews with patients; every question was asked for both cyclosporine and prednisolone separately at the same time.

**Data Collection**

Physicians referred eligible patients to the researcher in the clinic 2 days weekly, and the researcher collected the data. Informed consent was obtained from the patients, and then they were recruited into the study. The researcher would have asked patients the 8 MMAS questions for both cyclosporine and prednisolone. The data collection sheet was filled later from patients' medical records. All cyclosporine serum concentrations were documented from the first test after the patient's discharge from the hospital after HSCT. If the patients did not have any reported cyclosporine serum levels during the past 2 weeks, the patients' blood samples were taken. If the patients had more than one cyclosporine level in a month, the mean of these values was counted as the cyclosporine trough level. All the patients were using the same trusted laboratory based on the clinic's set of rules.

## RESULTS

A total of 110 eligible patients participated in the study. They were mostly men with a mean age of 32.5 years. The details of patient characteristics are listed in Table 1.

**Table 1:** Patient characteristics

| Characteristics | Measures | |
|---|---|---|
| Age, Mean±SD (range) | 32.5 ± 9.07 (18-58) | |
| Sex N (%) | Male | 65 (59.1) |
| | Female | 45 (40.9) |
| Education N (%) | Elementary | 9 (8.2) |
| | High school Diploma | 41 (37.3) |
| | Associate Degree | 13 (11.8) |
| | Bachelor and higher | 47 (42.7) |
| Marital Status N (%) | Single | 31 (28.2) |
| | Married | 79 (71.8) |
| Mean Time after allo-HSCT, month Mean±SD (range) | 2.75 ± 1.40 (1-6) | |
| Types of Malignancy | ALL | 34 (30.9) |
| | AML | 43 (39.1) |
| | M.M | 13 (11.8) |
| | CLL | 4 (3.6) |
| | A.A | 4 (3.6) |
| | F.A | 3 (2.7) |
| | H.L | 4 (3.6) |
| | NHL | 3 (2.7) |
| | Thalassemia Major | 2 (1.8) |
| Number of Drugs Mean ± SD (range) | AB | 2.86 ± 0.49 (2-5) |
| | Other Drugs* | 2.59 ± 0.81 (1-5) |
| | Total Drugs | 7.43 ± 0.94 (5-10) |

* Other than AB and immunosuppressant

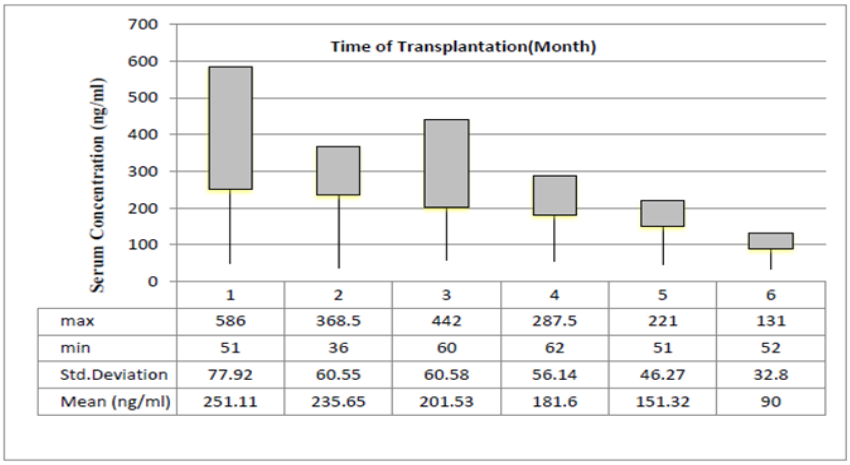
This study evaluated adherence to cyclosporine and prednisolone in 110 and 108 patients, respectively. All the patients answered all the questions. The calculated mean total scores for cyclosporine and prednisolone were 7.73 ± 0.62 and 7.63 ± 0.73, respectively. The details of their scores are shown in Table 2.

**Table 2:** Adherence level to medication regimen (the Eight-Item Morisky Medication Adherence Scale [MMAS-8])

| Adherence level* / Drug name | Low N (%) | Moderate N (%) | High N (%) |
|---|---|---|---|
| Prednisolone | 5 (4.6) | 25 (23.1) | 78 (72.2) |
| Cyclosporine | 4 (3.6) | 21 (19.1) | 85 (77.3) |

*Based on the Morisky manual

Based on the documented cyclosporine level for every patient from months 1 to 6 after HSCT, the mean of cyclosporine for each month was obtained. The details of cyclosporine levels of 110, 87, 55, 32, 14, and 5 patients from month 1 to month 6, respectively, are depicted in Figure 1.




| | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| max | 586 | 368.5 | 442 | 287.5 | 221 | 131 |
| min | 51 | 36 | 60 | 62 | 51 | 52 |
| Std.Deviation | 77.92 | 60.55 | 60.58 | 56.14 | 46.27 | 32.8 |
| Mean (ng/ml) | 251.11 | 235.65 | 201.53 | 181.6 | 151.32 | 90 |

Figure 1. Mean of cyclosporine serum level and its range

As can be observed, except for the sixth month, in all the other months, the patients had experienced toxic levels of cyclosporine (>200 ng/ml). Concentrations lower than the therapeutic level (<100 ng/ml) can be observed in all 6 months. In this period, a significant correlation was noticed between the adherence total score and cyclosporine serum concentration at the second-, third-, and fourth-month post-transplant ($r = 0.28$, $P = 0.014$; $r = 0.52$, $P < 0.001$; $r = 0.60$, $P = 0.001$). This finding means with increasing adherence, increased levels of cyclosporine were noticed in the second, third, and fourth months.

The mean of cyclosporine serum concentration levels was also assessed at different adherence levels. It was required to omit the low adherence level from the comparisons due to the small number of samples (only 1 sample in some cases). The results of Table 3 show that in the second, third, and fourth months, the mean cyclosporine serum concentration in the high adherence level was higher than the moderate adherence level. This difference was not significant in other months (all $P > 0.4$).

**Table 3:** Average of cyclosporine serum concentration in different month

| Month | Cyclosporine Serum Concentration Mean ± SD | Mann-Whitney Z | p |
|---|---|---|---|
| Second | | | |
| Moderate | 201.58 ± 54.03 | 40.19 | 0.008 |
| High | 240.44 ± 40.19 | | |
| Third | | | |
| Moderate | 146.21 ± 28.73 | -2.801 | 0.005 |
| High | 214.73 ± 39.58 | | |
| Fourth | | | |
| Moderate | 148.15 ± 33.54 | -4.093 | < 0.001 |
| High | 208.86 ± 40.33 | | |

Multiple linear regression analysis was used to test the association of the adherence score and the level of cyclosporine with controlling the confounding factors (i.e., gender, age, and marital status). The results of the regression indicated that a 1 score increase in the MMSA-8 would, on average, increase the cyclosporine level by 34.48 ng/ml with a confidence interval of 15.54-53.42 ($P < 0.001$).

Patients' characteristics were evaluated to find any association with adherence. Gender and educational level did not influence adherence to medication; nevertheless, the mean Morisky total score was higher among married subjects (Table 4).

**Table 4:** Average of Morisky score in different groups

| Factor | Morisky Total Score Mean±SD (Cyclosporine) | Statistic | p | Morisky Total Score Mean±SD (Prednisolone) | Statistic | p |
|---|---|---|---|---|---|---|
| | | | Sex | | | |
| Female | 7.71 ± 0.87 | -0.456* | 0.648 | 7.59 ± 0.73 | -0.345* | 0.730 |
| Male | 7.75 ± 0.61 | | | 7.66 ± 0.55 | | |
| | | | Marital Status | | | |
| Single | 7.56 ± 0.92 | -1.757* | 0.079[a] | 7.34 ± 0.78 | -2.431* | 0.015[b] |
| Married | 7.81 ± 0.61 | | | 7.74 ± 0.58 | | |
| | | | Educational Level | | | |
| Sikl | 7.41 ± 1.16 | 3.092** | 0.213 | 7.32 ± 1.29 | 3.425** | 0.180 |
| Diplom | 7.68 ± 0.67 | | | 7.48 ± 0.87 | | |
| Academic | 7.81 ± 0.46 | | | 7.77 ± 0.48 | | |

* Mann-Whitney Z , ** Kruskal Wallis Chi-Square, a: significance level 0.1, b: significance level 0.05

Further evaluations showed that there was no clinically significant correlation between the Morisky total score and the number of antibiotic drugs, other drugs, total number of drugs, and age.

## DISCUSSION

This study is one of the few studies about immunosuppressant drug adherence in post-HSCT patients using the MMAS-8 questionnaire. The medication poor adherence was observed to be 27.7% and 22.7% for prednisolone and cyclosporine, respectively. This amount of poor adherence is high due to the complexity of the BMT treatment process and its costs. Previous studies on the adherence rate after post-HSCT also confirm this poor adherence [1, 16]. It should also be considered that in those methods in which patients are questioned, the adherence level tends to be overestimated [2].

Previous studies on assessing post-HSCT adherence are limited [to 2, 7, 8, and 17]. There is only one pilot study (N = 33) that has used the MMAS-8 method to assess adherence to drugs in this population [1]. It was stated that about 45% were highly adherent to their GVHD prophylaxis regimen versus about 70% high adherence in the present study. The current study, with a three-time greater sample size, could provide more comprehensive results. The present study also assessed, particularly, cyclosporine and prednisolone; however, Lehrer et al. [1] used one questionnaire for the whole post-Allo-HSCT regimen (including up to 14 medications).

In a study by Hoodin et al. [20], which assessed post-HSCT patients' adherence through the patients' self-report, drug adherence was reported to be 94%. However, studies using methods other than patient reports have shown lower rates of medication adherence[10, 21]. There is one other study using the MMSA-4 for compliance assessment as one of the factors in post-HSCT patient screening and reporting that about half of the patients were non-adherent. Nevertheless, it has been stated that studies based on the MMAS-8 can better assess the conditions and behavioral considerations associated with adherence to medication. It also has better psychometric features [9, 22]. In general, the sensitivity and specificity of the MMAS-8 is higher than the MMAS-4 [9].

The present study showed that there was a direct correlation between cyclosporine concentration and medication adherence in the second, third, and fourth months. In total, the current study also demonstrated that with a 1 score increase in the MMSA-8, there would be about a 35 ng/ml increase in the cyclosporine blood level. Cyclosporine concentration plays a significant role in the incidence of acute GVHD [23]. Therefore, improving medication adherence in these patients can result in better cyclosporine concentration and better outcomes. However, it should also be considered that if a patient has an acceptable adherence but is still out of therapeutic range, the dose modification should be considered since the cyclosporine concentration

is affected by considerable intra-patient and inter-patient pharmacokinetics variability [6].

Cyclosporine levels less than 100 ng/ml were observed in all 6 months. Zeighami et al. stated that cyclosporine concentrations should be maintained even above 200 ng/ml to lower the incidence of acute GVHD [6]. In the aforementioned study, which was also performed on the Iranian population, the incidence of acute GVHD at concentrations below 200 ng/ml was 15%, and it would reach 3% at concentrations of 200 ng/ml and higher [6]. In addition, the present study showed that in the first 5 months after transplantation, some patients experience toxic cyclosporine concentrations higher than 200 ng/ml. These findings all highlight the importance of active dose adjustment.

Non-adherence to the medication has been noticed immediately after discharge. One of the reasons is the lack of proper patient education regarding the use of medication [24]. In studies by Barboza-Zanetti et al.[3], Chieng et al.[25], and Corrêa et al.[26], it is also shown that in post-medication therapy in HSCT, patient education regarding the role of each prescribed drug, using drugs properly, and possible side effects by pharmacists can increase the level of adherence and reduce the failure in drug therapy. This becomes more important when the patient's condition is asymptomatic and with prophylactic medication [1]. Chieng et al. showed that pharmacist intervention in post-HSCT medication therapy can reduce the MMAS-4 score even to 0 (equal to the highest score of the MMSA-8) [25].

The challenges patients and their families face when dealing with new conditions at home are another factor that leads to non-adherence to medication immediately after discharge [17]. In the present study, it was observed that the only significant sociodemographic characteristic that affects adherence was marital status. Married subjects have more adherence than single subjects. This finding is also supported by other studies [27-31].

The current study did not find any relationship between the number of drugs and the level of adherence. Lehrer et al.'s results [1] are similar to the results of the present study. However, other studies have reported a reduction in adherence by both increasing the number of drugs [32] and the lower number of prescribed medications in post-HSCT [7]. It has been stated that the number of doses per day in adherence to a drug is much more important than the number of drugs [8].

**Study Limitations**

This study has some limitations. In this study, 110 patients from a single center of transplant were involved. Although this sample well explains the rate of medication adherence, it was not sufficient to identify the factors involved in medication adherence in this population. Further multicenter studies with larger sample sizes are required to obtain more comprehensive information.

Secondly, the relationship between non-adherence and clinical outcomes was not in the scope of this study because the samples were hard-to-track outpatients, and good infrastructure was required for collecting patients' outcomes. Nevertheless, since the cyclosporine concentration plays a major role in the incidence of acute GVHD, this study tried to assess it for all patients and assessed its correlation and regression with patients' adherence. As Lehrer et al. have mentioned, adherence was evaluated by a self-questionnaire, which is susceptible to error. However, to minimize the potential errors, the present study also used a biochemical measure (i.e., cyclosporine blood level) as another valid and reliable method for assessing medication adherence to confirm the collected data[33].

**CONCLUSION**

Hematopoietic stem-cell transplantation imposes high costs on both the community and the patient. The present study showed a high prevalence of poor adherence to medication in post-Allo-HSCT patients. Cyclosporine plays the most important role after the Allo-HSCT period since it prevents GVHD. Moreover, this study indicated that its blood level directly correlates with patients' adherence, and with one score increase, the cyclosporine level also rises about 35 ng/ml on average. This means it is possible to have the optimal cyclosporine level for each patient by improving patients' adherence, along with proper dose monitoring and adjustment. Numerous predictors are known as non-adherence factors to

medication. Therefore, the current emphasis should be on factors that improve adherence, and future studies should focus on that since, in the post-HSCT population, there is not enough study about effective factors in patients' adherence.

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**CONFLICTS OF INTEREST**

The authors declared no potential conflict of interest.

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