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Immunosuppressive Medication Adherence in Kidney Transplant Recipients During the COVID-19 Pandemic: A Cross-Sectional Study in Hong Kong

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ABSTRACT

Background. The coronavirus disease 2019 (COVID-19) pandemic has put an enormous burden on health care systems worldwide. Limited access to medical care and fear of increased infective risks due to the use of immunosuppressive medication (IM) have increased concerns about IM adherence in kidney transplant recipients (KTRs). The aim of this study was to determine the various dimensions of IM nonadherence in KTRs during the COVID-19 pandemic.

Methods. This was a single-center, cross-sectional study using a convenient sampling approach. KTRs with follow-up in Queen Elizabeth Hospital, Hong Kong between May 1, 2020 and September 30, 2020, were invited to complete a self-reported questionnaire on IM adherence. The sociodemographic factors associated with IM adherence were extracted from medical records.

Results. Overall, 210 patients completed the questionnaires. The overall IM nonadherence rate was 35.2% in the 4 weeks before survey completion. None of the patients stopped taking IMs without instructions from their health care providers. The most common pattern of IM nonadherence was timing adherence ($n = 63$; 30.1%), followed by dose-skipping item. Among the different sociodemographic factors studied, only marital status was an independent risk factor of IM nonadherence (odds ratio, 1.97; 95% confidence interval, 1.04-3.72; $P = .03$).

Conclusions. The impact of COVID-19 on IM adherence in KTRs was not significant. All the patients continued their IM despite of the pandemic. Good family support can have a positive influence on treatment adherence in KTRs during the COVID-19 pandemic.

Kidney transplantation remains the mainstay of treatment for patients with end-stage kidney disease. A successful transplantation can offer a better quality of life when compared with those who remain on dialysis treatment [1]. However, a major concern in kidney transplantation is patient adherence to immunosuppressive medication (IM) [2,3]. Many studies have reported that medication nonadherence is a primary reason for graft failure in kidney transplant recipients (KTRs) [4,5].

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2. The COVID-19 pandemic is putting a huge burden on health care systems worldwide. To combat the current pandemic, different regions have carried out various measures including lockdowns and mobilization of health care workers to the frontline of the COVID-19 infection. As a result, those patients with

chronic diseases requiring regular follow-up may be affected because access to health care facilities and their attending physicians may be denied. Moreover, the worries of being infected in hospitals has discouraged many patients from returning to clinics for follow-up. The limited access to medical care in response to the outbreak is further increasing the concerns about medication adherence in KTRs. Additionally, it still remains unclear how to best manage IM in transplant recipients during COVID-19. Some patients might simply discontinue the IM owing to the fear of increased risks for infection and mortality related to

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COVID-19 [6,7]. Hence, a better understanding of IM adherence in KTRs during the pandemic is essential.

Nonadherence often is difficult to detect in clinical settings. Although clinical interviews, medical records, and drug levels have been used to measure drug adherence, the accuracy of these measures is not certain. Adherence ratings also can vary among different health care professionals. Additionally, drug-level measurements are influenced by various pharmacokinetic factors and can only reflect recent drug consumption [8]. Although electronic monitoring remains the most sensitive and valid measurement method of nonadherence, self-report questionnaires have been recommended as cost effective and convenient. Self-reported nonadherence is found to be significantly correlated with nonadherence assessed by electronic monitoring, which is viewed as the reference standard [9,10].

Although the importance of IM adherence in KTRs is well documented in the literature, IM adherence in these patients during the COVID-19 pandemic remains unknown. Therefore, to our knowledge, this is the first study to determine the various dimensions of IM nonadherence in KTRs during the COVID-19 pandemic and whether there are any sociodemographic factors that have influenced their behavior.

MATERIALS AND METHODS

This was a single-center, cross-sectional study using a convenient sampling approach. On March 11, 2020, the World Health Organization declared COVID-19 to be a pandemic. The study was conducted in KTRs during their routine follow-up visits at the outpatient clinic of Queen Elizabeth Hospital within the period between May 1, 2020 and September 30, 2020. Queen Elizabeth Hospital is 1 of the 4 major kidney transplant centers in Hong Kong SAR and 402 KTRs were cared by the center within the study period. During the pandemic, ~20% of the patients did not attend their scheduled follow-up appointments in an effort to avoid severe acute respiratory syndrome coronavirus 2 infection. However, all did have phone contact with nurses and then came back to “refill” their medications. The inclusion criteria included 1. age ≥ 18 years; 2. ≥ 6 months posttransplant; 3. functioning kidney graft; and 4. ability to communicate in Chinese language. Most of the patients were on triple IM including a calcineurin inhibitor (cyclosporine or tacrolimus), mycophenolate, or azathioprine and prednisolone. Patients on alternate regimen including a mammalian target of rapamycin inhibitor (sirolimus or everolimus) were also included in the present study. The study was approved by the Kowloon Central Cluster Research Ethics Committee and was carried out according to the Declaration of Helsinki. In the outpatient clinic, a well-trained renal nurse asked eligible patients if they would like to participate in a study on IM adherence. Those who signed a consent form were given a self-reported questionnaire to complete.

The Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS) was used to assess IM adherence in our study. The BAASIS was developed by the Leuven-Basel Research Group and has been widely used to measure IM adherence among kidney, heart, liver, and lung transplant recipients with established reliability and validity [11,12]. Permission to use the BAASIS has been granted by the University of Basel. The BAASIS was originally developed in English and has been translated previously into different languages (including simplified Chinese). In the present study, the BAASIS was translated into traditional Chinese for KTRs in Hong Kong. The questionnaire includes 4 questions that determine the implementation

dimension (dose taking, drug holiday, timing adherence, and dose alteration) and 1 on discontinuation dimension (stopped medication) of IM adherence in the 4 weeks before answering the survey. Overall nonadherence was defined as any positive response (“yes”) to the 5 questions. The sociodemographic and clinical parameters of the patients including age, sex, educational level, marital status, and posttransplant duration were all extracted from patient medical records.

Statistical analyses were performed by SPSS version 24 (IBM, Armonk, NY, United States). Categorical data were expressed as percentages and were compared with χ^2 or Fisher’s exact tests, whereas continuous data were expressed as mean \pm SD and were compared with *t* test. Relationship between sociodemographic data and IM adherence were analyzed with multivariate logistic regression analysis. All tests were 2-tailed, and differences for $P \leq 0.05$ were considered significant.

RESULTS

In all, 220 patients consented and participated in this study. Ten patients were excluded from the analysis because of incomplete questionnaires. Of the 210 patients who completed the BAASIS, 57.6% were male and the mean age was 56 ± 10.4 years. The median time after kidney transplant was 140 months (range, 6–362 months). Most of the patients were married (74.9%); 23.5% were single, and 1.6% were divorced/widowed. The sociodemographic characteristics of the patients are shown in Table 1. Among these patients, 202 (96.2%) were on prednisolone, 119 (56.7%) on twice-daily tacrolimus (Prograf), 20 (9.5%) on once-daily tacrolimus (Advagraf), 69 (32.9%) on Neoral cyclosporine, 55 (26.2%) on azathioprine, 122 (58.1%) on mycophenolate mofetil, and 17 (8.1%) on sirolimus.

From the 5-item BAASIS, the overall IM nonadherence rate was 35.2% ($n = 74$) in the preceding 4 weeks. These patients demonstrated problems with the implementation dimension of IM adherence. None of the patients stopped taking IM without instructions from their health care provider. Among the

Table 1. Sociodemographic Characteristics of Kidney Transplant Recipients

Variable	Adherence (n = 136)	Nonadherence (n = 74)	P Value
Age (y)	56.6 \pm 10.3	54.8 \pm 10.6	0.22
Sex, n (%)			0.63
Male	80 (58.8)	41 (55.4)	
Female	56 (41.2)	33 (44.6)	
Marital status, n (%)			0.03
Single/divorced/widowed	28 (20.6)	25 (33.8)	
Married	108 (79.4)	49 (66.2)	
Educational level, n (%)			0.94
Primary or less	20 (14.7)	12 (16.2)	
Secondary	95 (69.9)	50 (67.6)	
Tertiary	21 (15.4)	12 (16.2)	
Post-transplant time (y), n (%)			0.56
<5	28 (20.6)	11 (14.9)	
5-10	30 (22.0)	19 (25.7)	
>10	78 (57.4)	44 (59.4)	
Number of transplant, n (%)			0.55
First	127 (93.4)	71 (95.9)	
Second	9 (6.6)	3 (4.1)	

Table 2. Adherence to Immunosuppressive Medications Measured by BAASIS Questionnaire

Item Number		No. (%)
1A	Taking non-adherence: Yes/No	30 (14.3) / 180 (85.7)
	1 occasion	21 (10)
	2 or more occasions	9 (4.3)
1B	Drug-holidays: Yes/No	12 (5.7) / 198 (94.3)
	1 occasion	8 (3.8)
	2 or more occasions	4 (1.9)
2	Timing non-adherence: Yes/No	63 (30.1) / 147 (69.9)
	1 occasion	21 (10)
	2-3 occasions	31 (14.8)
	Every 2-3 days	7 (3.4)
	Almost every day	4 (1.9)
3	Dose-alteration: Yes/No	1 (0.5) / 209 (99.5)
4	Discontinuation: Yes/No	0 (0) / 100 (100)

BAASIS, Basel Assessment of Adherence to Immunosuppressive Medication Scale; IM, immunosuppressive medications.

different items in the questionnaire, the item “Have you taken your IM >2 hours before or after prescribed times in the last 4 weeks” was the most commonly cited (n = 63; 30.1%), followed by the dose-skipping item (Table 2). Considering the different sociodemographic characteristics studied, only marital status was found to have a statistically significant association with nonadherence (P = .03) (Table 1). Married patients had a better IM adherence than those who remained single or divorced/widowed. When the sociodemographic factors were entered into the multivariate logistic regression analysis, only marital status was an independent risk factor of IM non-adherence (odds ratio, 1.97; 95% confidence interval, 1.04-3.72; P = .03).

DISCUSSION

At the time of writing, there was only limited data concerning the impact of COVID-19 on the IM adherence in patients with chronic diseases, but none of them were in KTRs. Hence, to our knowledge, this was the first study to investigate IM adherence in KTRs during COVID-19 pandemic. IM nonadherence can be multifactorial and has been studied extensively in the nonpandemic setting [13]. At the time of COVID-19, shortage of drugs and fear of increased mortality associated with the immunosuppressive effects of medications were common reasons for IM nonadherence in patients with rheumatic diseases [6,7]. Although complete discontinuation of IM was the most common pattern of nonadherence in patients with rheumatic diseases [6], none of the KTRs in the present study stopped IMs completely without advice from their health care providers. This is probably because all the patients in the present cohort realized that IM discontinuation might lead to acute rejection and graft loss.

The prevalence of IM nonadherence in KTRs varies widely according to the different measurement tools and evaluation criteria, with empirical evidence reporting an average prevalence of 28% (range, 8%-65%) [14]. In an IM adherence study using the BAASIS questionnaire, 55% of KTRs delayed IM doses more commonly than skipping a dose (44% vs 26%) [13]. In another BAASIS study involving Chinese patients, 44.2% of KTRs were found to have IM nonadherence, with most related to timing adherence (41.8% of patients took the IM >2 hours before or after recommended dosing times in the previous 4 weeks), whereas only 1.9% of patients stopped the medication completely without instructions from their provider [15]. In the present study, 35.2% of the respondents were nonadherent to the IM in the 4 weeks before taking the survey, with all of them having implementation problems. In accordance with other studies [13,15,16], nonadherence with taking the IM and dosing nonadherence were low in the present cohort. For those patients who reported skipping IM doses, 70% only missed 1 dose in the 4-week time span. The most common pattern of IM nonadherence in the present study remained timing (30.1%). In fact, another study reported that ≤86.7% of KTRs could have problems with timing adherence [17]. Because forgetfulness is one of the main reasons for medication nonadherence [18], reducing the number of daily doses such as to a once-daily drug regimen may help improve medication adherence [16,19].

Among the various sociodemographic factors that might affect medication adherence, the present study found that KTRs who were single, divorced, or widowed had a significantly higher risk for IM nonadherence than those who were married. This finding corresponds to a previous study that also showed that marital status was a significant predictor of better IM adherence in KTRs [20]. In fact, family support has been shown to have a positive influence on treatment adherence in patients with chronic diseases [21,22]. This is particularly important as the COVID-19 pandemic continues. With concerns about the contagious nature of this virus, patients with chronic diseases are strongly advised to stay at home and avoid unnecessary social contacts even with family members, who often provide support for regular use of therapies. This has left many of these patients with anxiety and depression as a result of lockdowns and self-isolation [23]. The negative effects of stress on medication adherence have been well documented [24].

The present study had several limitations. One of the major concerns of self-reported questionnaires is socially desirable answers that may lead to an overestimation of adherence prevalence. Additionally, patients who are most likely suspected to have IM nonadherence are those who do not attend the clinics as scheduled and therefore are not represented in the present cohort. Moreover, other factors related to IM adherence such as self-efficacy, beliefs about medication, and therapy-related factors [13] were not explored in this study. Finally, this pandemic may last for a long time, and with cross-sectional nature of this study, it will be very difficult to study the overall impact of COVID-19 on the IM nonadherence of KTRs for a lengthy duration.

CONCLUSION

The impact of COVID-19 on IM adherence in KTRs was not significant compared with the results from the literature. A drastic change in behavior with regard to the use of IMs was not observed in the first few months of pandemic. None of the present study patients discontinued their IM without physician approval. The most common dimension of IM nonadherence remained timing. Among the different sociodemographic factors, marital status was the only significant predictor of IM adherence in these patients. Thus, good family support can have a positive influence on treatment adherence in KTRs during the COVID-19 pandemic.

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