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Commentary

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Old but Still a Significant Problem: Medication Nonadherence in Transplant Recipients

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To maintain long-term graft function, transplant patients must adhere to lifelong immunosuppressive therapy. Medication nonadherence (MNA) is one of the often underestimated and modifiable factors severely influencing graft survival.[1] Medication nonadherence accounts for approximately 16% of early graft losses and 20% of antibody-mediated rejections.[2] Donor-specific antibody (DSA) production may be associated with MNA. Medication nonadherence can also generate non-DSA anti-HLA (Human Leukocyte Antigens) long before developing DSA anti-HLA and antibody-mediated rejection.[3] Moreover, MNA is responsible for frequent hospitalizations and high healthcare costs.[4] Therefore, the Consensus on the Management of Modifiable Risk in Transplantation guidelines recommend identifying and monitoring at-risk kidney transplant recipients (KTR) for nonadherence to immunosuppressive drugs.[5]

DEFINITION OF NONADHERENCE

Medication adherence means taking the medication at the prescribed dose and time. Medication adherence can be quantitatively evaluated with the proportion of drug intake (taking adherence) or the proportion of correct dose intervals (timing adherence).[6] A "Nonadherence Consensus Conference" reported that MNA is "a deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect."[7]

It is helpful to classify MNA as intentional and nonintentional. Medication nonadherence is mainly nonintentional. Intentional MNA refers to the deliberate refusal to take prescribed drugs correctly. It may appear in a short time after transplantation or later during follow-up. This behavior covers nearly 14% of the KTR.[8]

Nonintentional MNA implies a nondeliberate behavior to missing the prescribed medications and involves 62% of KTR. Some of the patients with nonintentional MNA initially hide their mistakes. They eventually may become intentional nonadherent patients unless they experience a significant adverse event. A typical situation in these patients is the so-called "drug holiday," when a patient stops taking the medication temporarily.[2]

PREVALENCE OF NONADHERENCE

The prevalence of MNA can differ significantly, ranging from 2% to 67% in solid organ transplant recipients.[9] It has been reported that KTR are the most nonadherent among transplant recipients. Medication nonadherence is so common that almost a third of KTR may be nonadherent to immunosuppressive drugs.[4] A meta-analysis demonstrated that the prevalence of nonadherence to immunosuppressive drugs in KTR was higher than in other solid organ transplant patients (35.6 cases vs. 22.6 cases per 100 persons per year, respectively).[10] In

Turkish KTRs, Ordin et al[11] reported that the nonadherence rate to tacrolimus-based immunosuppression is 19.18%.

Electronic medication adherence monitoring reveals that MNA emerges early after transplantation, although its undesired effects are delayed.[6] Medication nonadherence increases with time elapsed since transplant, approximately 20% every 5 years after transplantation.[2]

RISK FACTORS FOR NONADHERENCE

The World Health Organization has defined 5 categories of risk factors to provide better insight into nonadherence to chronic disease treatment regimens: patient-related physical and psychosocial factors, disease-related factors, therapy-related factors, and socioeconomic and healthcare provider factors.[6] On the other hand, risk factors can be classified into 2 groups modifiable and nonmodifiable. While the physical characteristics of the patient and disease-related factors are usually nonmodifiable, interventions can improve modifiable factors such as therapy complexities and organizational issues. Other significant risk factors cover time since transplant, medication beliefs, patient lifestyle, health literacy, cognitive and learning capacities, competing priorities, sociocultural barriers, racial and ethnic minorities, low perceived health, and low social support.[1,2,10]

The most substantial risk factors include previous nonadherence and adolescence or young adulthood.[5-7] Constantiner et al[12] reported that younger age and lower income were significantly associated with MNA in a study that analyzed the medication adherence of 312 kidney transplant patients using a self-reporting questionnaire.

DIAGNOSING AND MONITORING NONADHERENCE

No method is the gold standard since every method used to diagnose and monitor MNA has advantages and disadvantages. In addition, despite using efficient methods to determine nonadherence, they may only sometimes be helpful in intentionally nonadherent patients. The most commonly used methods are direct and indirect: Direct methods cover directly observed medication administration, serum drug level monitoring, and a digestible sensor system embedded in pills. Indirect methods include monitoring pill counts and medication refills, self-reporting using validated questionnaires, and using microprocessors embedded in the drug container.[1,2,13] All these methods, if used individually, have poor sensitivity. However, although costly and time-consuming, these strategies can achieve high sensitivity and accuracy of adherence measurement if combined with serum drug level monitoring.[2,11] This method is called "triangulation."[14]

SELF-REPORTING QUESTIONNAIRES

The self-reporting method is beneficial as an initial examination and helps identify patients who need more careful evaluation, whereas it has an inherent underreporting bias.[15] Although combining measurement methods is suggested as the gold standard for measuring MNA, self-reporting questionnaires are usually considered an essential component of medication adherence. Despite the limitations of self-reporting questionnaires, including underreporting and social desirability bias, they are easy to use, inexpensive, and suitable as part of a combined measurement method.[16]

The best-known self-reporting questionnaires for measuring MNA in transplant patients are the Immunosuppressant Therapy Adherence Scale (ITAS) and the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS). The ITAS, developed by Chisholm et al[17] in 2005, is the first valid and reliable instrument to evaluate immunosuppressive therapy adherence after solid organ transplantation. The ITAS comprises 4 questions about immunosuppressant-taking behavior in the previous 3 months. It has been successfully applied in kidney transplant populations.[18,19] In 2016, the ITAS validity and reliability studies were performed by Madran et al[20] in kidney, liver, and heart transplant recipients and adapted for Turkish (ITAS-Tr). Immunosuppressive therapy adherence has been successfully evaluated using the ITAS-Tr in Turkish KTR.[11]

The BAASIS, developed by the Leuven-Basel Adherence Research Group at the University of Basel in 2005, is one of the most appropriate questionnaires for use in adult and adolescent transplant recipients.[16] The scale, currently translated into 11 languages, is available in 2 versions: The BAASIS Interview (self-report) (recommended) and the BAASIS Written self-report.[15] The BAASIS assesses measurements regarding immunosuppressive drug use, i.e., taking adherence, timing adherence, drug holidays, and dose reduction. It is also comparatively shorter than other self-reporting questionnaires for measuring MNA in transplant recipients.[16]

Compared with the BAASIS, the ITAS evaluates medication adherence within the last 3 months, and it was developed in a hypertensive population.[11,16] The BAASIS follows the taxonomy of medication adherence which defines adherence as "the process by which patients take their medication as prescribed." According to this definition, adherence to a medication regimen covers 3 interrelated stages: initiation, implementation, and (dis)continuation.[21] The latest BAASIS version is a 6-item scale evaluating initiation (1 item), implementation (4 items), and discontinuation (1 item). Initiation and discontinuation stages are queried over a 1-year reminding period, whereas the implementation stage questions include the last 4 weeks.[15]

The BAASIS has been widely applied to kidney and other solid organ transplant recipients in research and clinical practice to measure medication adherence.[22,23] Language-specific validation studies were performed in Brazilian-Portuguese and Japanese.[24,25] Most recently, the BAASIS validity has been analyzed psychometrically in a meta-analysis including 26 studies providing data on 12 109 transplant recipients. The instrument

demonstrated good validity and reliability in assessing MNA in transplantation.[15]

In the current issue, Oruç and colleagues assessed the reliability and validity and provided a transcultural adaptation of the BAASIS to measure adherence to immunosuppressive drugs in Turkish KTRs.[26] The authors preferred to adapt the BAASIS Interview version as recommended by the Leuven-Basel Adherence Research Group. A total of 125 (41.1% deceased donor) adult kidney recipients on tacrolimus (60.5%), cyclosporine (26.6%), and everolimus (12.9%)-based immunosuppressive therapy were included in the study. They performed psychometric tests for reliability (Kappa coefficient and Cronbach's alpha) and validity (content and construct validities) of the BAASIS.

The authors demonstrated good reliability and validity of the BAASIS to assess adherence to immunosuppressive drugs with sufficient Kappa coefficient >0.9 and acceptable Cronbach's alpha coefficient of 0.454. Content validity results were adequate, with no doubts of understanding, whereas for construct validity, adequate factorial loads for all questions (1a, 2, 3, and 4) were obtained if question 1b was excluded.

The primary limitation of this study is the low Cronbach's alpha coefficient of 0.454. The authors explained that although a Cronbach's alpha coefficient above 0.7 is preferred, in some cases, low alpha coefficient levels may still be helpful.[27] Additionally, several factors can affect the coefficient value, such as the number of items in the questionnaire, the number of participants, the type of items/answers, and the homogeneity of the study group.[28]

Taken together, this validated scale can contribute to a practical approach to measuring adherence to immunosuppressive drugs and contribute to developing interventions to improve adherence. After that, the validated Turkish version of the BAASIS should be applied further in the studies, including larger transplant patient populations, to verify. Moreover, it is reasonable to think that the validated instrument will also help measure medication adherence in patients with other solid organ transplants. However, further studies will be necessary to confirm this assumption.

WAYS TO IMPROVE MEDICATION NONADHERENCE

Medication adherence interventions have significantly increased adherence to immunosuppressive drugs in solid organ transplant recipients.[9] However, limited studies have effectively addressed MNA in KTR and its critical impact on graft survival. Medication nonadherence prevention and treatment interventions cover clinical pharmacist care, treatment simplification, reduction of pill burden, remote monitoring, telemedicine, medication reminder intervention, and educational-behavioral intervention.[2,8,13]

Clinical pharmacists may be included in medication adherence monitoring by supervising direct drug delivery, counseling, and evaluating the MNA using 1 validated questionnaire.[2] In different studies investigating the impact of a clinical pharmacist on medication adherence in KTR, a significant increase in overall adherence was observed.[29-32] Moreover, Chisholm et al[29] determined a significantly lower number of graft rejections. One of these studies, a randomized controlled trial conducted by Joost et al.[31] found that clinical pharmacist care increased taking adherence percentage during the first posttransplant year (95% vs. 82% for intervention and controls, respectively, $P < .006$). However, rates for rejections in both groups were not different ($P = .54$). Another randomized controlled trial investigating the influence of pharmaceutical care, including 128 KTR, reported no difference in tacrolimus coefficient of variation, calculated from 6 dose-corrected whole blood tacrolimus trough concentrations (31.4% vs. 32.5%) and a questionnaire-based medication adherence rate (27% vs. 25%).[33]

In the current issue, the study conducted by Yucel[34] and colleagues involved the clinical pharmacist in monitoring medication adherence using the ITAS in KTRs and aimed to identify the factors related to MNA. A total of 100 adult kidney recipients on tacrolimus (67 patients), cyclosporine (26 patients), and everolimus (7 patients)-based immunosuppressive regimens were included in the study.

The prevalence of MNA varies widely in solid organ transplant recipients, ranging from 2% to 67%, depending on the definitions and measurement instruments used.[9] According to studies evaluating nonadherence by self-report, the mean prevalence in KTR was 27.7%.[4] This study found the MNA rate is relatively high, especially in patients using tacrolimus (67.1%). The high MNA rate in this study may be due to the high ITAS cut-off value, distinguishing between medication adherence and nonadherence. Moreover, in nonadherent (ITAS ≤ 11) recipients, time since transplant was more prolonged than in adherent recipients (ITAS = 12) (median 79 months vs. 48 months, $P = .041$, respectively). As time elapsed since transplant increases, it becomes more difficult for KTR to maintain medication adherence.[35]

In this study, the most common problems with adherence to immunosuppressive drugs identified by the clinical pharmacist were an inappropriate time of drug administration (64.0%) and forgetting to take medications (25%). Although the effect of clinical pharmacists' involvement was not evaluated in this study, integrating clinical pharmacists in monitoring medication adherence may be beneficial in identifying MNA, increasing medication adherence, and decreasing the likelihood of being hospitalized and associated costs in KTR. Because of the small number of KTR included in this study, especially in the everolimus group, there is a need for studies with a more significant number of patients also involving clinical pharmacists.

CONCLUSION

Nonadherence to immunosuppressive drugs after transplantation, an old problem, still maintains its importance today. Early diagnosis and treatment of nonadherence can prevent early and late post-transplant graft dysfunction. For this purpose, using the instruments, e.g., validated questionnaires, and cooperating with clinical pharmacists may be beneficial, especially in recipients at risk of nonadherence to immunosuppressive drugs.

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