Research Letter

Prevalence of Medication Nonadherence to Co-medication Compared to Immunosuppressants in Heart Transplant Recipients: Findings From the International Cross-sectional BRIGHT Study

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ABSTRACT

Purpose: To assess and compare the prevalence of medication nonadherence (MNA) (implementation and persistence) to immunosuppressants and co-medications in heart transplant recipients.

Methods: MNA prevalence was assessed using the Basel Assessment of Adherence to Immunosuppressive Medications Scale (self-report) and compared using logistic regression in a 4-continent sample of 1397 heart transplant recipients from 36 heart transplant centers in 11 countries.

Findings: MNA was significantly ($\alpha = 0.05$) higher to co-medications than to immunosuppressants (taking nonadherence: 23.9% vs 17.3%; odds ratio [OR] = 1.5; 95% CI, 1.30−1.73; drug holiday: 5.7% vs 1.9%; OR = 3.17; 95% CI, 2.13−4.73; dose alteration: 3.8% vs 1.6%; OR = 2.46; 95% CI, 1.49−4.06; and discontinuation: 2.6% vs 0.5%; OR = 5.15; 95% CI, 2.36−11.20).

Implications: The observed MNA necessitates adherence-enhancing interventions encompassing the entire post−heart transplant medication regimen. ClinicalTrials.gov identifier: NCT01608477. (*Clin Ther*. 2019;41:130−136)

Keywords: co-medications, cross-sectional, heart transplantation, immunosuppressants, international, medication adherence.

INTRODUCTION

Heart transplant recipients depend on complex lifelong medication regimens,[1] including immunosuppressants to prevent graft rejection and other long-term co-medications (eg, antihypercholesterolemics [98.3% of all patients take statins 5 years after heart transplant][2] and antihypertensives [81.8% of all patients take angiotensin-converting enzyme inhibitors or angiotensin receptor blockers 5 years after heart

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transplant][2]) to treat preexisting comorbidities or to prevent or treat post–heart transplant comorbidities.[1] Previous research indicates that heart transplant recipients' mean total number of medications at discharge was 14.3.[2] Five years post-HTx, all patients showed polypharmacy and 32% of patients were taking 16 medications or more (i.e. Tx medications, co-medications and over the counter drugs), many administered more than once daily. This high treatment burden increases the risk of medication nonadherence (MNA).[3] In solid organ transplantation,[4] MNA is defined as any "deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect" and is associated with suboptimal clinical and economic outcomes.[4]

As a process, medication adherence consists of 3 phases[5]: initiation, implementation, and persistence. For heart transplant recipients, initiation occurs during hospitalization for transplantation, making it irrelevant in the context of nonadherence. Implementation nonadherence involves multiple dimensions[6]: taking nonadherence (missing ≥1 dose), drug holiday (skipping ≥2 consecutive doses), timing nonadherence (taking medication >2 h before or after the prescribed time), and dose alteration (taking more or fewer pills than prescribed or changing dosages without a physician's order).

Although considerable transplantation research has been devoted to immunosuppressant nonadherence, co-medication nonadherence is less studied. Four heart transplant studies[7–10] reported separate prevalence estimates of co-medication nonadherence but without distinguishing among the phases of adherence. This omission impedes identification of target behaviors for interventions. To the best of our knowledge, the only study[11] to investigate the prevalence of implementation nonadherence to both medication categories in heart transplant recipients reported overall implementation nonadherence prevalence of 36.7% and 39.2% to immunosuppressants and co-medications, respectively. However, that study's single-center design limited the generalizability of its results to the heart transplant population.

Accordingly, assessing MNA to immunosuppressant and co-medication implementation and persistence in a diverse sample of heart transplant recipients from various countries while distinguishing between the various adherence dimensions will clarify how heart transplant recipients manage their post–heart transplant medication regimens and help identifying target behaviors for adherence-enhancing interventions. Therefore, the central aims of this study were to describe and compare the prevalence of MNA (in the implementation and persistence phases) to immunosuppressants and co-medications in an international sample of heart transplant recipients.

METHODS

This study is a secondary data analysis of the Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (BRIGHT) study, a cross-sectional study in 36 heart transplant centers in 11 countries on 4 continents. Detailed information on the BRIGHT study's methods is reported elsewhere.[12]

Sampling and Data Collection

The data were collected via patient interviews during outpatient clinic visits. Using a stratified random sampling approach based on center size (number of annual heart transplant procedures), heart transplant recipients were eligible to participate if they were adults (≥18 years old at enrollment), had received their transplants and were undergoing follow-up for routine care at a participating heart transplant center, received a heart transplant as a single-organ transplant, were first-time heart transplant recipients, were at 1–5 years after heart transplant, were able to read and understand one of the languages in which the study was conducted, and were willing and able to provide written informed consent. Heart transplant recipients were excluded if they had participated in adherence-intervention research or drug trials during the 6 months before inclusion or had received professional support for medication intake.

Variables and Measurement

Implementation- and persistence-phase MNA was assessed during the patient interview (self-report) based on a recall period of 4 weeks for implementation and 1 year for persistence. The instrument used was the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS©),[6] which is built around the most recent taxonomy for medication adherence.[5] Administered in a nonthreatening, nonjudgmental manner to encourage truthful answers, the BAASIS© starts by asking the patient's about their current immunosuppressant regimen (ie, each medication's

name, dose, dosing frequency, and intake schedule). The MNA assessment process is described below.

Assessment of MNA to Immunosuppressants

Implementation is covered by 4 yes/no items: taking nonadherence, drug holiday, timing nonadherence, and dose alteration. Persistence is measured by asking patients if, during the recall period, they stopped taking their medication completely without physician's orders (yes/no).

Assessment of MNA to Co-medications

The BAASIS© instrument was adapted for co-medications for which taking nonadherence, drug holiday, and dose alteration are the only assessed implementation dimensions because timing nonadherence is less critical for most of these medications. Persistence to co-medications was assessed as with immunosuppressants.

Scoring of the BAASIS©

Within each of the measured MNA dimensions, each positive answer indicated an instance of MNA. To indicate the prevalence of nonadherence within each dimension, we calculated the percentage of heart transplant recipients answering positively. In addition, for immunosuppressants, a positive answer to any of the implementation dimensions indicated an instance of overall implementation nonadherence (summarized similarly as a percentage).

Statistical Analysis

Data were summarized descriptively based on levels of measurement and distribution (ie, frequencies, proportions, means [SDs]). To avoid overrepresentation or underrepresentation of each country's heart transplant recipient population, MNA prevalence was calculated as a weighted mean. This was achieved by multiplying each national nonadherence prevalence by a weighting factor corresponding to the ratio of the heart transplant recipient population in the corresponding country to that of all included countries during the period of the study's data collection there (based on data from the Global Observatory on Donation and Transplantation, http://www.transplant-observatory.org).

To compare immunosuppressant and co-medication nonadherence prevalence, we used logistic regression analysis by generalized estimation equations, adjusting for data clustering on the heart transplant recipient and center levels. Because <2% of data were missing, pairwise deletion was used. The significance level was set at 0.05. STATA statistical software, version 13 (StataCorp LLC, College Station, Texas) was used for descriptive statistics and

Table 1. Sample characteristics

Characteristic	Value
Age (N)	1380
Years, mean (SD)	53.7 (13.2)
Gender (N)	1390
Male, n (%)	1011 (72.7%)
Ethnicity (N)	1381
Caucasian, n (%)	1186 (85.9%)
Education (N)	1377
Primary school, n (%)	187 (13.6%)
Secondary school, n (%)	426 (30.9%)
Further education, n (%)	294 (21.4%)
University, n (%)	470 (34.1%)
Employment status (N)	1391
Employed, n (%)	413 (29.7%)
Marital status (N)	1387
Single, n (%)	242 (17.5%)
Married/cohabiting, n (%)	955 (68.9%)
Divorced/separated, n (%)	149 (10.7%)
Widowed, n (%)	41 (3%)
Time post-HTx (N)	1395
Years, mean (SD)	3.4 (1.4)
Immunosuppressants (N)	1389
Calcineurin inhibitors	1325 (95.4%)
Tacrolimus, n (%)	879 (63.3%)
Cyclosporine, n (%)	452 (32.5%)
IMDH inhibitors	1127 (81.2%)
Mycophenolate, n (%)	1066 (76.7%)
Azathioprine, n (%)	61 (4.4%)
Corticosteroids	710 (51.2%)
Prednisolone, n (%)	698 (50.3%)
Hydrocortisone, n (%)	13 (0.9%)
mTOR inhibitors	263 (19%)
Everolimus, n (%)	199 (14.3%)
Sirolimus, n (%)	64 (4.6%)

N = number of patients with observations for the corresponding variable; SD = standard deviation; IMDH = inosine monophosphate dehydrogenase; mTOR = mechanistic target of rapamycin.

Table II. Prevalence and comparison of MNA, implementation and persistence phases, to immunosuppressants and co-medications.

Adherence Dimension	Prevalence of MNA (BAASIS©) for Immunosuppressants[a]			Prevalence of MNA (BAASIS©) for co-medications[a]			Logistic Regression Results	
	n/N	% Observed	% Weighted (95% CI)	n/N	% Observed	% Weighted (95% CI)	OR (95% CI)	*P*
Implementation[b]								
Taking	241/1392	17.3	15.1 (13.2–17.0)	333/1392	23.9	21.2 (19.0–23.3)	1.50 (1.30–1.73)	<0.0001
Drug holiday	26/1392	1.9	1.4 (0.8–2.0)	79/1392	5.7	5.1 (3.9–6.2)	3.17 (2.13–4.73)	<0.0001
Timing	395/1376	28.7	26.2 (23.9–28.5)					
Dose alteration	22/1387	1.6	1.5 (0.8–2.1)	53/1390	3.8	4.0 (3.0–5.0)	2.46 (1.49–4.06)	0.0004
Overall implementation	520/1392	37.4	34.5 (32.2–37.2)					
Persistence[c]								
Discontinuation	7/1386	0.5	0.6 (0.2–1.0)	35/1390	2.6	2.4 (1.6–3.2)	5.15 (2.36–11.20)	<0.0001

BAASIS© = Basel Assessment of Adherence to Immunosuppressive Medication Scale; MNA = medication nonadherence; OR = odds ratio.

[a] MNA prevalence was calculated as a weighted mean by multiplying each national nonadherence prevalence by a weighting factor corresponding to the ratio of the heart transplant recipient population in the corresponding country to that of all included countries during the period of the study's data collection there (based on data from the Global Observatory on Donation and Transplantation, http://www.transplant-observatory.org) as follows: $Weighted\ sample\ MNA\ prevalence = \sum_{k=1}^{n} Country_k Sample\ MNA\ prevalence \times (Country_k HT_x - recipient\ true\ population\ count\ during\ the\ study\ recruitment\ period\ in\ the\ country \div HT_x - recipient\ true\ population\ count\ of\ all\ countries\ during\ the\ study\ recruitment\ period\ in\ all\ countries)$.

[b] Dimensions were as follows: taking dimension, omitting a single dose once or more during the prior 4 weeks; timing dimension, taking the medication >2 h before or after the prescribed taking time once or more during the prior 4 weeks, only for immunosuppressants; dose alteration dimension, altering the prescribed amount of medication once or more during the prior 4 weeks without a physicians' order; and drug holiday dimension, skipping at least 2 consecutive doses once or more during the prior 4 weeks.

[c] Discontinuation of medication use completely within the prior year without a physicians' order.

SAS statistical software, version 9.4 (SAS Institute Inc, Cary, North Carolina) for regression analysis.

RESULTS

From the 36 participating heart transplant centers, 2523 patients were eligible for inclusion. We randomly invited 1677 to participate, of whom 1397 (83.3%) responded. Their characteristics are given in Table I. The observed and weighted prevalence of MNA for immunosuppressants and co-medications is reported in Table II.

Medication Nonadherence to Immunosuppressants

Calcineurin inhibitors were used by 95.4%, inosine monophosphate dehydrogenase inhibitors by 81.2%, corticosteroids by 51.2%, and mechanistic target of rapamycin (MTOR) inhibitors by 19% of the sample. Immunosuppressant implementation nonadherence was observed in 37.4% of participants. More specifically, the immunosuppressant nonadherence prevalence was 17.3% for taking nonadherence, 1.9% for drug holiday, 28.7% for timing, and 1.6% for dose alteration. For discontinuation, we found a prevalence of 0.5%.

Medication Nonadherence to Co-medications

The prevalence of nonadherence to co-medications was 23.9% for taking nonadherence, 5.7% for drug holiday, 3.8% for dose alteration, and 2.6% for discontinuation.

Comparison Between Immunosuppressant and Co-medication Nonadherence

We found significantly higher levels of nonadherence to co-medications than to immunosuppressants (taking non-adherence: odds ratio [OR] = 1.50; 95% CI, 1.30−1.73; $p < 0.0001$; drug holiday: OR = 3.17; 95% CI, 2.13−4.73; $p < 0.0001$; dose alteration: OR = 2.46; 95% CI, 1.49−4.06; $p = 0.0004$; and discontinuation: OR = 5.15; 95% CI, 2.36−11.20; $p < 0.0001$). Similar higher prevalence of co-medication nonadherence was also observed at the national level in all countries and dimensions except the taking dimension in Belgium and Switzerland.

DISCUSSION

This study found, in a large international sample of heart transplant recipients, that post−heart transplant MNA is prevalent for both immunosuppressants and co-medications. Given the risk accompanying immunosuppressant nonadherence vis-à-vis heart transplant outcomes[4,8] and the limited forgiveness of immunosuppressants,[4] this magnitude of MNA is worrisome and calls for interventions. Moreover, confirming the evidence from prior studies in heart transplant[11] and other transplant populations,[13] we found significantly higher prevalence of MNA to co-medications than to immunosuppressants. A study in kidney transplant recipients[13] proposed the concept of self-regulation as an explanation (ie, patients might classify their drugs according to their indication to 2 categories [strict vs flexible] and adjust their medication intake accordingly based on the daily pill burden). This adjustment/regulation process is conceptualized[14] as a function of the representation of health threats, the targets set accordingly for ongoing coping, the procedures to regulate these targets, and the appraisal of coping outcomes. Whether this self-regulation model sufficiently explains the observed adherence differences remains to be confirmed.

This study has some limitations. First, given the main study's many variables and large sample, MNA was measured via self-report, which is susceptible[15] to social desirability and memory biases. Second, the main study's focus was on immunosuppressants. Accordingly, detailed data on individual co-medications (eg, number and names of drugs, daily pill burden) were unavailable for this secondary analysis. For the same reason, investigating factors responsible for the sample's differential MNA was beyond the main study's scope. Third, centers were eligible for inclusion only if they had performed a mean of ≥10 heart transplant procedures annually. Smaller centers might organize post−heart transplant care differently, possibly resulting in different MNA prevalence. Fourth, timing and, hence, overall implementation nonadherence could not be measured for co-medications, meaning no direct comparison with immunosuppressants was possible across all MNA dimensions. To summarize, our findings of significantly higher nonadherence to co-medications than to immunosuppressants call for further investigation of its underlying reasons and for the integration of adherence assessment and enhancement interventions for all medications in post−heart transplant care.

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CONFLICT OF INTEREST STATEMENT

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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