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LETTER TO THE EDITOR

Medication nonadherence to immunosuppressants after adult allogeneic haematopoietic stem cell transplantation: a multicentre cross-sectional study

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Following allogeneic haematopoietic stem cell transplantation (HSCT), adherence to immunosuppressants (IS) is crucial to prevent and treat chronic GvHD (cGvHD), which is associated with reduced quality of life, increased morbidity and mortality, and increased overall health-care needs.[1] According to Vrijens'[2] taxonomy of medication nonadherence (MNA), it can be defined as a deviation from the prescribed medication regimen sufficient to adversely influence the regimen's intended effect. This may involve late or non-initiation of the prescribed treatment, suboptimal implementation of the dosing regimen (taking; drug holidays; timing; dose reduction), early discontinuation of treatment or any combination of these.[2] Although studies in the HSCT population are lacking, evidence in oral anti-tumour CML treatment shows alarming prevalences of up to 85.8%.[3,4]

Identifying patients at risk of MNA and developing adherence-enhancing interventions for them demands an understanding of the underlying reasons for nonadherence. Therefore, the aims of this study were: (1) to describe the prevalence of different forms of MNA, (2) to examine associations between MNA and selected correlates and (3) to explore the association between immunosuppressive MNA and cGvHD.

This report is a secondary data analysis of the multicentre cross-sectional PROVIVO study investigating patient-reported outcomes of long-term survivors after allo-HSCT (NCT01275534).[5] Convenience sampling was used to recruit allogeneic HSCT recipients from the University Hospitals of Basel and Zurich between November 2011 and November 2012. Detailed descriptions of the PROVIVO researchers' data collection procedures are described elsewhere.[5]

In accordance with Vrijens'[2] taxonomy, the six-item 'Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS)'[6] was used to measure patients' self-reported IS medication adherence on different dimensions (for example, initiation, implementation—taking, dose reduction, timing, drug holiday—discontinuation) over the preceding 4 weeks.[2] Patients' medication adherence was also assessed by a senior physician from each of the two centres. On the basis of IS blood tests, a personal review of patients' medication intake behaviour, the senior physician noted whether a subject seemed to have been fully adherent (YES = adherent / NO = nonadherent).[6]

On the basis of these measures a composite MNA adherence score was created for each patient. Patients were classified as nonadherent if they reported nonadherence on at least one of the six BAASIS items (for example, taking, timing and so on) and/or were identified as nonadherent by the physician assessment. Clinical and demographic variables were retrieved from patients charts and the transplant database. In order to describe the prevalences of the different dimensions of MNA we used descriptive statistics. Second, a univariate binary logistic regression was applied in order to examine associations between MNA and selected clinical correlates. A full record of variables is shown in Table 2. The clinical variables were selected based on the author's literature review on possible risk factors for MNA in haematology. Factors arising from the univariate analysis that revealed significant *P*-values (< 0.05) were entered in an additional multivariate binary logistic regression model. For our third aim we used multivariate binary logistic regression to explore the association between immunosuppressive MNA and cGvHD.

Of 638 eligible HSCT recipients in follow-up care, 376 (58.9%) participated. Of these, 99 (26.3%) were taking IS medications and were, therefore, included. Table 1 presents demographic and clinical characteristics of patients both in total and grouped by adherence/nonadherence.

The prevalence of MNA along the different dimensions of medication taking was the following: 64 patients (64.6%) showed some kind of nonadherence, of these, 33.3% of patients had missed at least one IS dose in the past 4 weeks. Three patients (3.2%) reported drug holidays, that is, missing at least two consecutive doses. Timing nonadherence occurred in 61.2% of cases, meaning that they took their medications more than 2 h early or too late. Four patients (4.1%) reduced their medication doses on their own and three patients (3.1%) discontinued their medication intake without asking their physician.

Physicians reported nonadherence in 18 patients (18.9%). Combining patients' self-reported MNA with physicians' assessments yielded a nonadherence prevalence of 68.7% across the entire sample, 62.2% in patients with no/mild cGvHD and 80.2% in patients with moderate/severe cGvHD. Binary regression analysis correlated MNA significantly with higher numbers of daily taken IS pills (odds ratio (OR): 1.42; 95% confidence interval (CI): 1.08–1.87; $P = 0.011$) and with immunosuppressive therapies using either calcineurin inhibitor alone or calcineurin inhibitor steroid combinations, as well as with a lower number of daily prescribed concomitant medications (OR: 0.85; CI: 0.74–0.98; $P = 0.024$). Ordinal logistic regression showed a positive association between MNA and higher grades of cGvHD (OR: 3.01; CI: 1.27–7.14; $P = 0.012$), Table 2.

This is the first study to describe an association between cGvHD and MNA. A high prevalence of MNA was shown, particularly regarding timing and taking. Surprisingly, not only patients taking higher numbers of IS agents, but also those taking lower numbers of concomitant medications were more likely to be nonadherent.

Current evidence regarding solid organ transplant patients indicates clear associations between small deviations from prescribed immunosuppressive medication schedules and poor clinical outcomes[6] (for example, deviations $>5\%$ from dosing schedules has been associated with increased incidences of graft loss or late acute rejection in renal and heart transplant recipients). However, no information is available on a deviation threshold for diminished outcomes in HSCT. Therefore, further prospective research is needed to develop a clinically meaningful definition of IS MNA, and to explore possible causal relationships between dosing schedule deviations and poor clinical outcomes in the HSCT population.

Importantly, this study adds MNA as a behavioural pathway to the genetic and biophysiological components of cGvHD

Table 1. Demographic and clinical characteristics ($N = 99$)

Characteristics	*Total N = 99*	*Nonadherent[a] n = 65*	*Adherent n = 34*
Age, median (IQR; range)	51.0 (18.7; 20.3–71.8)	51.0 (19.4; 20.8–71.8)	53.0 (15.6; 20.3–68.1)
Years after HSCT, median (IQR; range)	3.9 (5.0; 1.0–29.0)	4.0 (4.7; 1.0–29.0)	3.9 (5.9; 1.0–26.0)
Gender; male, *n* (%)	61 (61.6)	42 (64.6)	19 (55.9)
Marital status, n (%)			
Married or cohabited	75 (75.8)	49 (75.4)	26 (76.5)
Haematological diagnosis, n (%)			
Acute leukaemia (AML, ALL)	49 (49.5)	33 (50.8)	16 (47.1)
CML / MDS / MPS	22 (22.2)	14 (21.5)	8 (23.5)
Lymphoma / CLL / MM	27 (27.2)	17 (26.2)	10 (29.4)
Non-malignant haematologic disease	1 (1.0)	1 (1.5)	0 (0.0)
Status of haematological disease, n *(%)*			
CR	92 (92.9)	63 (96.9)	29 (85.3)
Myeloablative treatment regimen (conditioning), *n* (%)	75 (76.5)	52 (81.3)	23 (67.6)
TBI[b], n (%)			
Yes	65 (66.3)	44 (68.8)	21 (61.8)
Donor relationship, n (%)			
Unrelated	52 (52.5)	35 (53.8)	17 (50.0)
Identical sibling or matched related	44 (44.4)	29 (44.6)	15 (44.1)
Mismatched related	3 (3.0)	1 (1.5)	2 (5.9)
cGvHD[c], n (%)			
No	22 (22.7)	10 (15.6)	12 (36.4)
Yes	75 (77.3)	54 (84.4)	21 (63.6)
Not documented[d]	2 (2.0)	1 (1.5)	1 (2.9)
cGvHD grade in cases (n = 75) according to NIH criteria			
Mild	39 (52.0)	26 (48.1)	13 (62.0)
Moderate	27 (36.0)	20 (37.0)	7 (33.3)
Severe	9 (12.0)	8 (14.8)	1 (4.8)
Functional impairment[e], n (%)			
80–100%	80 (82.5)	55 (87.4)	25 (73.5)
< 80%	17 (17.5)	8 (12.7)	9 (26.5)
Not documented	2 (2.0)	2 (3.1)	0 (0.0)
Immunosuppressive regimen, n (%)			
Steroids[f] only	11 (11.6)	3 (4.8)	8 (25.0)
CNI (CYA or tacrolimus) only	48 (50.5)	33 (52.4)	15 (46.9)
Others (mTOR inhibitor or mycophenolate)	5 (5.3)	3 (4.8)	2 (6.3)
Combination (+ steroids[e])	31 (32.6)	24 (38.1)	7 (21.9)
Not documented	4 (4.0)	2 (3.1)	2 (5.9)
Number of IS pills, median (IQR; range)	2.5 (2–4.25; 1–12)	3.0 (2.0–5.0; 1–10)	2.0 (1.25–3.75; 1–12)
Number of concomitant medications, median (IQR; range)	8.0 (5.0–10.0; 1–22)	8.0 (5.0–10.0; 1–14)	9.0 (6.0–11.0; 1–22)

Abbreviations: cGvHD = chronic GvHD; CNI = calcineurin inhibitor; CYA = cyclosporine A; HSCT = haematopoietic stem cell transplantation; IQR = interquartile range; IS = immunosuppressants; MDS = myelodysplastic syndrome; MM = multiple myeloma; MPS = myeloproliferative syndrome; mTOR = mammalian target of rapamycin; NIH = National Institutes of Health. [a]Nonadherence is any YES answer on any of the five items of the BAASIS. [b]Prevalence of patients who had a TBI in the conditioning regime with 12 Gray. [c]cGvHD was rated by the physician with the cGvHD grading scheme recommended by the National Institutes of Health consensus development project on criteria for clinical trials in cGvHD. [d]Not reported are missing data and show valid percentages. [e]Functional impairment using the Karnofsky Performance Status was determined by the physician at the annual follow-up visit and comprises a scoring of individual's health and physical functionality based on criteria-related performance index rated from 100% (normal function) to 10% (moribund). [f]Prednisone with a dosage of at least 2.5 mg per day.

Table 2. Correlates of composite MNA in univariate and multivariate analyses

	Adjusted model for transplant centre		
	OR (95% CI)	*df*	*P-value*
Univariate binary logistic regression[a] (N = 99)			
Age	0.985 (0.952–1.019)	1	0.373
Gender	0.533 (0.220–1.289)	1	0.162
Years after HSCT	0.984 (0.903–1.073)	1	0.714
Number of daily taken IS pills	1.328 (1.042–1.694)	1	0.022
Immunosuppressive regimen		3	0.067
CNI (CYA or tacrolimus) only[b]	5.513 (1.175–25.857)	1	0.030
Others (mTOR inhibitor or mycophenolate)[b]	2.650 (0.253–27.781)	1	0.416
Combination (+ steroids)[c]	8.560 (1.623–45.159)	1	0.011
Number of daily taken concomitant medications	0.871 (0.766–0.990)	1	0.035
Functional impairment[d]	1.016 (0.987–1.047)	1	0.282
Depressive symptomatology	0.860 (0.271–2.733)	1	0.798
Nausea	0.801 (0.519–1.235)	1	0.314
Multivariate binary logistic regression[a] (N = 99)			
Higher number of IS pills is associated with MNA	1.422 (1.083–1.867)	1	0.011
Lower number of concomitant medications is associated with MNA	0.852 (0.742–0.979)	1	0.024
Transplant centre is associated with MNA	0.174 (0.055–0.553)	1	0.003
The explained variance of the adjusted model is acceptable (Nagelkerke R^2: 22.7%).			

Abbreviations: CI = confidence interval; CNI = calcineurin inhibitor; CYA = cyclosporine A; df = degrees of freedom; HSCT = haematopoietic stem cell transplantation; IS = immunosuppressants; MNA = medication nonadherence; mTOR = mammalian target of rapamycin; OR = odds ratio; WHO = World Health Organization. [a]Outcome variable for the regression analyses were the composite MNA adherence score. For the univariate binary logistic regression, correlates were selected based on the WHO adherence model and evidence of the literature regarding risk factors for MNA in haematology.[3,4] [b]Reference category: steroids. [c]Prednisone with a dosage of at least 2.5 mg. [d]Functional impairment using the Karnofsky Performance Status was determined by the physician at the annual follow-up visit and comprises an individual's health and physical functionality based on a criteria-related performance index rated from 100% (normal function) to 10% (moribund).

pathophysiology. Given the expected growth of GvHD patient numbers (resulting from the increased use of mobilised peripheral blood HSCT, reduced conditioning regimens, broader indications for mismatched/unrelated donors and older HSCT recipients) further understanding of this risk factor is crucial. Also, the heterogeneous nature of the disease is only partially understood: the absence of evidence-based second- and third-line management options poses further challenges.[7–9]

So far, only a few clinical trials have integrated medication taking measurements in their study designs. Determining what part of GvHD outcome variability is due to issues in immunosuppressive taking behaviours will call for the inclusion of medication adherence as a vital parameter in HSCT research.

Our study identified two therapy-related factors associated with MNA: 'number of daily taken IS pills' (positive correlation) and 'number of daily taken concomitant medications' (inverse correlation).

Although barriers to regular IS intake might include the unpleasant smell and taste of pills or cGvHD involvement of the mouth, one possible explanation for the inverse correlation between numbers of concomitant medications and MNA might be

that patients with fewer concomitant medications pay less attention to their medication management. Research in solid organ transplantation[10] indicates that barriers to adherence are often unintentional (for example, forgetfulness/interruption of daily routine) or determined by patients' attitudes (for example, the belief that not all IS are necessary to prevent rejection).[11] Clinicians recognise that patients consciously or unconsciously reduce or omit IS intake, potentially leading to cGvHD exacerbation. Clinical experience shows that some patients with treatment refractory disease eventually lose their belief in their medications' effectiveness ('the drugs don't work').[12]

However, whatever the reasons behind MNA, supporting patients' medication management is a key task for transplant teams. Throughout the long-term process of post-treatment follow-up, multidisciplinary teams collaborate to improve patients' HSCT outcomes. For example, a nurse-coordinated intervention programme, integrated within systems of care, could offer an opportunity to assess medication-taking behaviours and initiate individually tailored adherence-enhancing interventions with components proven to be effective against MNA, for example, brief (maximum one page) written medication adherence instructions, electronic reminders to take medications regularly, assistance with dose modifications, coaching for self-monitoring and side effect management.

Also, as developing and initiating state-of-the-art adherence interventions will demand an appropriately skilled clinical work force, it will be essential to integrate medication adherence-related topics into health-care providers' on-going education and training, and to support and evaluate innovative care approaches.

The findings of this secondary analysis must be interpreted in the context of potential limitations. The small sample size of this cross-sectional study allows only a small set of study variables and limits the statistical power. Concerning measurement accuracy, although combining self-report questionnaires with physicians' collateral reports results in greater sensitivity than either alone, the additional use of electronic monitoring would have provided the greatest possible sensitivity in detecting MNA.[13]

To conclude, our study demonstrated a high prevalence of MNA in the studied HSCT population, and established, for the first time, a positive association between MNA and cGvHD. Our findings call for future research of the behavioural dimension of cGvHD management, including the development and testing of a set of adherence-enhancing interventions, for routine application at HSCT centres.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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