Non-adherence assessment to immunosuppressant therapy with a self-report questionnaire and intra-patient variability in renal transplantation: risk factors and clinical correlations

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Non-adherence assessment to immunosuppressant therapy with self-report questionnaire and intra-patient variability in renal transplantation: risk factors and clinical correlations

Running title:

Non-adherence in renal transplantation

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Abstract

Background. Non-adherence (NA) to immunosuppressive drugs is to date considered a crucial issue in kidney transplanted patients (KTs), leading to de novo donor-specific anti-HLA antibodies (dnDSA) development, acute and chronic rejection, and at least graft loss. However, NA assessment is extremely challenging often leading to underestimation in real-life settings.

Methods. NA evaluation in all KTs referred to our post-transplantation clinic in the period between 01/01-15/07/2018 with self-report questionnaire combined to intra-patient variability (IPV) of pivotal immunosuppressive drug (tacrolimus/mTOR inhibitor)

Results. Based on both questionnaire and IPV 86 out of the 504 tested KTRs (17%) were classified as NA. Male gender (OR, 2.0 ; 95% confidence interval [CI], 1.2 to 3.4), high educational level (OR for KTRs with a degree, 1.8 [95% CI, 1.0 to 3.1]), employment status (OR, 2.0 [95% CI, 1.2 to 3.3]), young age at transplantation (p=0.017), longer time on waiting list (p= 0.027), and after transplantation (p= 0.049) were all associated to NA.

High IPV was mostly documented in KTRs treated with twice-daily formulation of immunosuppressive drug (OR, 1.5 [95% CI, 1.0 to 2.1]) and associated to dnDSA appearance (OR, 2.1 [95% CI, 1.1 to 3.9]).

Conclusions. NA is a significant problem, difficult to assess, and can lead to dnDSA development also in our population. Risk factors identification is kindly requested to stratify patients at high-risk allowing interventions for adherence improvement.

Keywords: non-adherence; self-report questionnaire; intra-patient variability of immunosuppressants; kidney transplant; donor specific antibodies

Text

Introduction

Medication Adherence is defined as "the extent to which the patient's behavior matches the prescriber's recommendations"[1]. The counterpart non-adherence (NA) to immunosuppressive drugs is to date considered as one of the widespread problem in the field of renal transplantation, leading to de novo donor-specific HLA antibodies (dnDSA) development, acute and chronic rejection, and at least graft loss[2,3].

The evaluation of NA is now consequently acquired a greatest importance. Different methods have been developed but, apart from directly observed therapy, every test has intrinsic limitations. Electronic monitoring, the gold standard, is expensive and unable to verify if pills have really been ingested[4]; pills count may be difficult to monitor in clinical practice, and bring no information about effective ingestion time[5]; self-reporting, the cornerstone of adherence assessment[6], is inexpensive and simple but can overestimate adherence[4]; physicians' opinion tends to underestimate NA[7]; the intra-patient variability (IPV) of serial trough levels could be associated to biological causes rather than NA, and patients may increase their medication dose only at the time of laboratory testing[8]. All these considerations partially justify the significant heterogeneity of NA prevalence, ranging from 2 to 65% in all organ recipients[9].

The aim of this study is to determine prevalence and risk factors of NA to immunosuppressive medication in our kidney transplant population with a combination of tests (self-reporting questionnaire and IPV) also evaluating its impact on dnDSA development and rejection episodes.

Material and Methods

Study design and included population

All consecutive patients who referred to our post-transplantation outpatient unit for a routine medical examination between the 1st of January and the 15th of July 2018 were considered eligible for this study. Patients received all information during their standard clinical visit (normally scheduled on 1, 3, 6 or 12 months after previous appointment depending on clinical conditions and transplantation period). Immunosuppressive regimens included the standard of care for transplanted patients (tacrolimus, cyclosporine, sirolimus/everolimus adjusted on trough blood concentrations and combined with mycophenolate and/or steroids). We excluded patients who were unable to understand the protocol and/or written italian language, and also subjects within the first 6 months after transplantation in order to avoid any bias in drug blood variability due to the frequent dose adaptations in the early post-transplantation period.

Clinical data were collected from medical records and included socio-demographic (gender, nationality, age at transplantation, level of education, employment status, presence of family support, residence, distance from the referring hospital), condition-related (pre-transplant treatment modality, type of dialysis, time on dialysis, donor type, number of previous transplantations, combined transplants, waiting time on the active list, time since transplantation) and therapy-related variables (number of prescribed immunosuppressants, number of dosing times of immunosuppressants). We also recorded results of all for-cause kidney biopsies performed during patients' clinical course (revised according to Banff Criteria [10]) and determination of dnDSA, if available (Luminex, MFI > 3000).

The study was performed in adherence with the last version of the Helsinki Declaration and with the Principles of the Declaration of Istanbul on Organ Trafficking and Transplant Tourism. All patients signed an informed consent before self-report questionnaire and IPV evaluation. This study is covered by Ethical Committee approval, resolution number 1449/2019 ("TGT" observational study).

Adherence evaluation

NA was assessed with a combined model that included a self-report questionnaire (similarly to Siegal et al[11] and Denhaerynck et al[12]) and IPV. Patients were asked if, in the previous four weeks, they had skipped or changed their immunosuppressive medications at least once. We than considered for every patient the intra-patient coefficient of variation (CV) of the last 4 serum trough levels of most important immunosuppressive drug in their therapeutic regimen (cyclosporine A, tacrolimus, or sirolimus/everolimus), according to the following equation:

$$CV\ (\%) = (SD/\mu) \times 100$$

where SD is the standard deviation and μ is the mean medication concentration of the four samples. We only considered trough levels measured during follow-up as outpatients (tests during hospitalization were excluded).

Patients were defined non-adherent (NA) if gave an affirmative answer to the item and had a high IPV (we used the median variability of the drug as the cut-off value, as suggested by Borra et al)[13].

Statistical analysis

Statistical analysis was performed with SPSS (IBM SPSS Statistics, vers. 25.0.0). Continuous variables are presented as mean ± standard deviation or as median (interquartile range (IQR) or min-max), according to their distribution analysed with Kolmogorov-Smirnov test. The difference between groups was analysed, respectively, with t-test or Mann-Whitney test. Some cut-off levels were with ROC curves.

Categorical variables are presented as fraction and Pearson's χ^2 or, for small samples, Fisher's exact test was employed to compare groups. The odds ratios (OR) with 95% Confidence Interval (CI) were used as a measure of relative risk.

Significance level for all tests was set at $p<0.05$

Results

A total of 505 KTRs were eligible for our study. Eighty-six out of 504 patients (17%) resulted as NA based on the self-report questionnaire and IPV (CV ≥ 19%) results (one patient was excluded due to low number of available through levels). As reported in Literature [13,14], a close correlation between self-reporting and IPV was not observed: an agreement in NA definition was obtained only in 266 cases (53%) (Kappa coefficient 0.061).

Clinical characteristics of studied population are summarized in Table 1. Analyzing patients' related factors, NA KTRs were more often men (75.6% in NA group vs 60% in adherence group; p=0.007, OR, 2.0; 95% confidence interval [CI], 1.2 to 3.4) and workers (42.6% vs 60.5%, p= 0.003; OR, 2.0 [95% CI, 1.2 to 3.3]) with a younger age at transplant (45.3±15 vs 49.4±13.9 years, p=0.017) and higher educational level (15.1% vs 11.5% with a degree and 51.2% vs 36.4% with a high school grade respectively, p= 0.003).

Considering transplant-related factors (Table 2), NAs have experienced a longer time both on waiting list (17.6 vs 10.4 months; p= 0.027) and after KT (9.6 years vs. 6.8 years; p= 0.049).

Main maintenance immunosuppressive therapies and immunological data are presented in Table 3. Majority of patients were treated with calcineurin inhibitors (tacrolimus -TAC- in 416/505 patients and cyclosporine in 65/505) followed by mTOR inhibitors in 24/505. Among them, once-daily formulation for both TAC and mTOR inhibitors showed a significant reduced IPV (43.8% vs 53.2% twice-daily tablets, p=0.049; OR for CV ≥ 19%, 1.5 [95% CI 1.0 to 2.1]).

In patients who underwent a for-cause kidney biopsy (167/505, 33.1%) no difference was noted in rejection rates, despite patients with significant IPV tend to be more frequently biopsied (36.9% vs 39%; p=0.067). Interestingly, in KTRs with high IPV de-novo DSA were detected in higher percentage (18.8% in CV ≥ 19% vs 9.7% in CV <19%, p= 0.012; OR, 2.1 [95% CI, 1.1 to 3.9]) (Figure 1).

Discussion

Medication adherence, especially to immunosuppressive drugs, is a crucial factor for allograft survival[4,5]. On the other hand, NA assessment is extremely challenging often leading to underestimation of this problem in real-life settings[7]. In our analysis we tried to identify NA in our outpatients using two combined techniques (self-report questionnaire and IPV), evaluating both risk factors and possible consequences of NA.

Firstly, we found that patient-reported NA and IPV were not associated with each other: the prevalence of NA based on questionnaire and combined evaluation with IPV was 31% and 17%, respectively. These data are similar to whom reported by other Authors[13,14] where discrepancies, as probably in our study, were correlated to the evidence that questionnaires evaluate the adherence to the whole immunosuppressive regimen, while IPV is only focused to the pivotal immunosuppressant[15,16].

Based on our adopted and more stringent definition, NA in our population were mostly man, with a younger age, workers and of a high educational level.

Comparing these characteristics to Literature data, male gender has been associated to reduced adherence[17] despite a systematic review recently tone down its independent role[18]. Young recipients (<50 years) were considered a high-risk group, maybe because have less perception of their risk of rejection or are less afraid to return to periodic dialysis. Furthermore, younger patients are more likely to be occupationally and socially active[6,17,19]. Some studies also showed that employed patients were more prone to forget medications or taking them late[6,17,19], and that illiterate recipients were paradoxically better monitored and managed than KTRs with a high scholar degree[20,21]. On the other hand, work and educational level are interdependent variables, as also showed by our results were most of the patients with a degree were also workers.

We also investigated the role of transplant and pre-transplant variables in NA; among them, time on waiting-list was significantly longer in the NA group. As expressed by other Authors, this may reflect that the perceived impact of transplant on life (including consequences of NA) and

emotional response to transplantation significantly decreased over time[21,22]. Per contrast, period on dialysis between adherent and NA patients did not differ. Few studies focused on dialysis role, with similar results[21].

As expected, twice-daily formulation was a risk factor for a high drug IPV: once-daily medications have clearly demonstrated to enhance adherence[23,24] and confer a lower risk of high CV[2]. This evidence appears as crucial considering that in our population dnDSA, a major cause of late allograft failure, were detected more often in patients with a high IPV, emphasizing the suggested role of high CV in underimmunosuppression, activation of alloimmune response and, consequently, DSA development[25].

Based on the significant consequences of NA, also in our real-life setting, predicting which patients may be at risk for NA would allow targeted interventions[26]. Since NA is a complex and multifactorial issue, a multimodal approach[9] should be used to improve patient compliance combining educational/cognitive interventions (transmission of information and knowledge), counseling/behavioral methods (modification of incorrect behaviors) psychologic/affective techniques (increase patient social relationships and supports)[27].

Furthermore, adherence strategies should address the cause of NA, i.e. forgetfulness in our experience. Cedillo-Galindo el al noted favorable results with the use of a cell phone alarm or alarm clocks, schedules, drug record book, and both making the medication visible on the table or taking drugs at meals[28]. Obviously, simplification of the therapeutic regimen switching to once-daily medications may enhance adherence[23]; however, some patients already intentionally reduced the dosage of immunosuppressants (especially corticosteroids) to avoid side effects[29]. In these situations, understanding patients' perception of adverse events is essential for accurate education and strategy adoption to enhance quality of life[30].

At least, also if all approaches to increase adherence failed, the stratification of NA population allow clinician to identify patients at high-risk of allograft disfunction. In this context an individualized approach (i.e. frequent DSA monitoring, protocol biopsies) may be recommended.

Conclusion

NA is a significant problem and can lead to dnDSA development with subsequent allograft failure also in our real-life experience. All detected risk factors (male gender, younger age at transplantation, high educational level, being employed, twice-daily medication, length of waiting list) suggest which patients are at risk of NA allowing targeted interventions.

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Notes

Conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract form. All the authors declare that they have no competing interests.

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Authors' contribution.

Alberto MELLA, Maria Cristina TORAZZA, Daniela FINOCCHIETTI: concept design, data collection, analysis and interpretation, and drafting article; Fabrizio FOP: statistics; Anna ALLESINA, Caterina DOLLA, Roberta GIRAUDI: data analysis and interpretation, and drafting article; Luigi BIANCONE: concept design, analysis and interpretation, and critical revision. All authors provided intellectual content of critical importance to the work described and approved the final version.

Data availability. All data and datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Figure Layout. Figure 1 is created and digitalized in high resolution by A.M. with BioRender.com.

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Tables

Table 1. Socio-demographic characteristics of studied population

	Adherent	**Non-Adherent**	**Total population**	**p value**
Adherence evaluation*, n (%)	418 (83)	86 (17)	504	
Gender, n (%)				
Woman	167 (40)	21 (24.4)	188 (37.4)	**0.007**
Man	251 (60)	65 (75.6)	316 (62.6)	
Nationality, n (%)				
Non-Italian	31 (7.4)	6 (7)	37 (7.3)	0.887
Italian	387 (93.6)	80 (93)	467 (92.7)	
Age at transplantation, years (SD)	49.4 (13.9)	45.3 (15.0)	48.6 (14.1)	**0.017**
Age at transplantation - groups, n (%)				
< 30 years	36 (8.6)	12 (14)	48 (9.5)	0.211
30 – 50 years	181 (43.3)	42 (48.8)	223 (44.4)	
50 – 70 years	185 (44.3)	29 (33.7)	214 (42.4)	
>70 years	16 (3.8)	3 (3.5)	19 (3.7)	
Family support, n (%)				
Yes	343 (82)	75 (87.2)	418 (83)	0.275
No	75 (18)	11 (12.8)	86 (17)	
Residence, n (%)				
Intra-region	376 (90)	79 (91.9)	455 (90.3)	0.795
Extra-region	42 (10)	7 (8.1)	49 (9.7)	
City	181 (43.3)	40 (46.5)	221 (43.8)	0.585
Outside the city	237 (56.7)	46 (53.5)	283 (56.2)	
Distance from the referring hospital, n (%)				
< 15 Km	306 (73.2)	67 (77.9)	373 (73.9)	0.663
≥ 15 Km	112 (26.8)	19 (22.1)	131 (26.1)	
Educational level, n (%)				
Degree	48 (11.5)	13 (15.1)	61 (12.1)	**0.003**
High school diploma	152 (36.4)	44 (51.2)	196 (39)	
Education for 8 years	147 (35.2)	26 (30.2)	173 (34.3)	
Education for 5 years	71 (16.9)	3 (3.5)	74 (14.7)	
Employment status, n (%)				
No workers	240 (57.4)	34 (39.5)	274 (54.5)	**0.003**
Workers	178 (42.6)	52 (60.5)	230 (45.5)	

*combination of self-report questionnaire and IPV

Table 2. Transplant-related factors in studied population.

	Adherent (n=418)	**Non-Adherent (n=86)**	**Total population (n=504)**	**p value**
Pre-transplant treatment modality, n (%)				
Pre-emptive	28 (6.7)	3 (3.5)	31(6.2)	0.259
Dialysis	390 (93.3)	83 (96.5)	473 (93.8)	
Hemodialysis	327 (83.8)	71 (85.5)	398 (84.1)	0.701
Peritoneal Dialysis	63 (16.2)	12 (14.5)	75 (15.9)	
Time on dialysis, years (IQR)	3.1 (1.6–5.6)	3.2 (1.7–5.6)	3.1 (1.6–5.6)	0.893
Number of previous renal transplants, n (%)				
None	367 (87.8)	78 (90.7)	445 (88.3)	0.732
1	43 (10.3)	7 (8.1)	50 (9.9)	
2	8 (1.9)	1 (1.2)	9 (1.8)	
Donor type, n (%)				
Living	21 (5)	6 (7)	27 (5.4)	0.464
Deceased	397 (95)	80 (93)	477 (94.6)	
Combined transplant, n (%)				
Yes	29 (7)	5 (5.8)	34 (6.7)	0.705
No	389 (93)	81 (94.2)	470 (93.3)	
Waiting time on the active list, months (IQR)	10.4 (3.3-29.6)	17.6 (6.0-40.4)	11.5 (3.8-31.8)	**0.027**
Time since transplantation, years (IQR)	6.8 (2.9-13.5)	9.6 (3.3-15.6)	7.4 (3.0-13.9)	**0.049**

Table 3. Therapy-related factors according to IPV or IPV + self-report questionnaire

	IPV evaluation (n = 502)			**Combined evaluation of self-report questionnaire and IPV (n = 504)**		
	CV < 19% n= 250	**CV ≥ 19% n=252**	**p-value**	**Adherent n=418**	**NA n=86**	**p-value**
Number of ID/day, n (%)						
1	29 (11.6)	27 (10.7)	0.942	47 (11.2)	10 (11.6)	0.992
2	138 (55.2)	139 (55.2)		231 (55.3)	47 (54.7)	
3	83 (33.2)	86 (34.1)		140 (33.5)	29 (33.7)	
Type of medication formulation, n[a] (%)						
Once-daily	91 (36.4)	71 (28.2)	**0.049**	141 (33.7)	23 (26.7)	0.208
Twice-daily	159 (63.6)	181 (71.8)		277 (66.2)	63 (73.3)	
Renal biopsies, n (%)						
Yes	73 (29.2)	93 (36.9)	0.067	136 (32.5)	31 (36)	0.529
No	177 (70.8)	159 (63.1)		282 (67.5)	55 (64)	
Histological finding on renal biopsies, n (%)[b]						
Rejection	22 (30.1)	41 (44.1)	0.131	53 (39)	11 (35.5)	0.119
Glomerulonephrtis	12 (16.4)	16 (17.2)		19 (14)	9 (29)	
Other	39 (53.4)	36 (38.7)		64 (47)	11 (35.5)	
dnDSA, n (%)[c]						
Tested	196 (78.4)	186 (73.8)		318 (76)	65 (75.6)	
Positive	19 (9.7)	35 (18.8)	**0.012**	43 (13.5)	11 (16.9)	0.473
Negative	177 (90.3)	151 (81.2)		275 (86.5)	54 (83.1)	

IPV: intra-patient variability; CV: intra-patient coefficient of variation; NA: non-adherent; ID: immunosuppressive drugs; dnDSA: de novo donor-specific antibodies

[a] For the pivotal drug in maintenance therapy (tacrolimus or mTOR inhibitors)

[b] Percentage on total biopsied patients

[c] Percentage on total tested patients

Title of Figures

Figure 1. Prevalence of de novo donor-specific antibodies (DSA) and difference between patients with high or low intra-patient variability (IPV) of pivotal immunosuppressive drug