Immunosuppressant treatment adherence, barriers to adherence and quality of life in renal and liver transplant recipients in Spain

Morales JM, Varo E, Lázaro P. Immunosuppressant treatment adherence, barriers to adherence and quality of life in renal and liver transplant recipients in Spain.

Abstract: To assess the adherence to immunosuppressant therapy (IST) and perceived barriers affecting IST adherence and quality of life (QOL) in patients who had received a renal (RT) or liver transplant (LT), a questionnaire was sent to over 9000 RT and LT recipients in Spain. Questionnaire comprised questions about patient’s socio-demographic, organ transplant and medication characteristics; IST adherence and patient’s perceived barriers to adherence; and patient’s QOL using the EuroQol. Data from 1983 RT patients and 1479 LT patients were analyzed. Self-reported adherence to IST in RT (92.6%) and LT (88.5%) recipients was high. Daily medication intake (mean of 2–3 doses/d per patient) was considered a lifestyle restriction in about 25% of transplant recipients and was the most common barrier to adherence perceived by over 30% of RT and LT patients. Overall, high-intensity treatment regimens were associated with poorer QOL (EuroQol < 70) compared with low-intensity treatment regimens. Most RT (71.0%) and LT (61.4%) patients would prefer to suppress the evening dose if they were able to. Although high adherence rates to IST were reported in this first large Spanish survey in RT and LT patients, adjustment of daily treatment intensity by less frequent dosing may be an adequate strategy to minimize barriers to adherence and improve QOL.

Nearly 1 million people worldwide have benefited from successful organ transplantation, and a significant proportion of patients can now expect to achieve a long-term survival with a high quality of life (QOL) (1). Improvement in survival has been possible mainly due to surgical and medical advances including prophylaxis of infectious diseases and the development of immunosuppressive drugs (such as tacrolimus and mycophenolate mofetil) and strategies to prevent transplant failure. However, non-adherence to immunosuppressant therapy (IST) leads to an increased incidence of acute rejection, chronic rejection and graft loss (2–5). Non-adherence is often subtle (subclinical) and unintentional; it may occur early and/or late after transplantation and tends to increase with time (2, 6). A correlation between subclinical non-adherence and the occurrence of late acute rejection has been reported (7). Recently, a reduction in graft life over the longer term has been observed even in patients with small non-adherence rates of 1.5–5% (6). Adherence to treatment is influenced by several factors related to patient’s lifestyle, socio-demographic and psychosocial characteristics or to the treatment regimen itself, which can act as either barriers or facilitators and constitute the main predictors of medication adherence (8–10).

Rates of non-adherence reported in international studies vary widely among all types of transplant recipients (3, 4, 8, 11). For renal transplant (RT) recipients, Butler et al. (3) found a median of 22% (18–26%) of non-adherent recipients in a systematic review of 36 studies, but it can even be higher (up to 68%) in some groups (12). For liver transplant (LT) recipients, lower rates of IST non-adherence (6.7% per yr) were found compared with RT recipients (35.6% per yr) in a meta-analysis of seven LT and 32 RT studies on
medication adherence conducted by Dew et al. (13). However, rates up to 39% have been reported in LT patients when non-adherence was considered as a late intake (±48 h) (9, 14). In Spain, non-adherence to treatment in RT patients has been insufficiently described (15, 16). Fernandez et al. (15) estimated a low rate of non-adherence in RT recipients (2% for all medication or 1% when only IST is considered). The different adherence rates observed in the Spanish studies compared with international studies can be due to methodological issues (e.g., method used to assess adherence) and social factors (gratuity of medication, higher medical and family support, etc.). No data are available about adherence in LT patients in Spain.

Despite the relevance that treatment adherence has for transplant survival, there is a lack of detailed and current information on the IST adherence in RT or LT patients in Spain. This study aimed to assess IST adherence and identify perceived barriers that affect adherence, as well as patient’s QOL in adult patients who had received a RT or LT.

Patients and methods

Setting and data collection

Data were obtained from a self-administered questionnaire adapted to Spain, which was responded anonymously. Subjects were eligible for participation if they aged 20 yr or older and were members of the Spanish association of renal patients “ALCER” or the “National Federation of Hepatic and Liver transplant patients” (FNETH) who had received either a RT or a LT. Transplant recipients were invited to participate in the survey through the above-mentioned associations. The questionnaire was sent to all FNETH members (about 4000), and to 5000 numbers randomly selected from the total number of ALCER members (15 734), maintaining the sample size of each geographical location proportional to the number of members.

For every included patient, a computerized data record form (containing socio-demographic, clinical, and the questionnaire information) was completed and an independent double-check was carried out.

The questionnaire comprised 32 questions about patient’s socio-demographic, organ transplant and medication characteristics, IST adherence and patient’s perceived barriers to adherence, as well as patient’s perceived QOL. The final questionnaire adapted to Spain was preliminary tested in 10 RT and 10 LT recipients to be considered suitable.

Questionnaire characteristics

Socio-demographic data included patient’s age, sex, marital status, education level, and working status. Organ transplant characteristics included time since first transplant. Medication characteristics included, among others, the number of daily drugs, tablets, and daily doses (DDs; medication intake); type of IST received; IST side effects; patient’s lifestyle restriction with daily IST intake (in a 0–10 scale: “0 = no restriction; 10 = highly restricted”); patient’s preference for dosing schedule; and patient’s concern about the number of IST doses (0–10 scale) and IST dosing schedule (0–10 scale) to override organ rejection. For analysis purposes, patients were grouped in different clusters according to the treatment intensity (number of mean daily drugs, tablets, and DDs of medication) received and afterward were further classified as low-intensity or high-intensity regimens.

Patient’s self-perceived health status was also inquired by using the EuroQol-5D (EQ-5D) instrument (EQ descriptive system, EQ visual analogue scale [EQ VAS], and EQ index score according to Spanish validated preferences), which is described elsewhere (17).

Adherence to IST was assessed according to answers to the question: “How many times did not you take your IST in the last month?” To assess transplant patients’ perceived barriers to IST adherence, we used a modified version of the Immunosuppressant Therapy Barrier Scale (ITBS) (18). The resulting scale included 12 items (eight items for “uncontrollable barriers” and four items for “controllable barriers”). “Uncontrollable barriers” refers to those barriers that patients may perceive to be beyond their control, that is, “to take the IST medication too many times per day,” whereas “controllable barriers” refers to barriers that should be under patients’ control with non-adherence occurring because of carelessness or deliberate intention not to adhere, that is, “I sometimes skip doses of my IST medication when I feel good (or better).” One of the items (item 13 of the original validated scale) exploring drug costs for the patient was deleted in the final questionnaire as it was considered not applicable for Spain where medication is subsidized by the Spanish health care system (HCS). Also, the number of answers for each item was reduced from 5 to 3 (from completely agree to completely disagree) to facilitate questionnaire’s understanding. The final score was 12 points for minimum and 36 points for maximum in the global scale, from 8 to 24 in the uncontrollable scale, and from 4 to 12 in the

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controllable scale. Minimum values meant less barrier presence.

Subjects
Calculation of sample size estimated that 2000 patients in total would be necessary for each of the RT and LT populations. About 1400 patients would be obtained assuming a response rate of 70%. This sample size allowed the detection of differences in adherence of 7% between subgroups with a 0.05 probability of type I (alpha) error and a statistical power of 0.8.

Statistical analyses
A descriptive analysis of the patient’s medication characteristics, adherence, barriers to adherence, QOL, and other relevant questionnaire variables was performed. In each transplant group, bivariate associations were analyzed. To compare groups, chi-square test was used for categorical variables. To compare continuous variables among groups, the distribution normality was checked using the Kolmogorov–Smirnov test, and the variance homogeneity using the Levene’s test. As the distributions of ITBS and EuroQol, that is, the variables compared among the treatment intensity groups, were not normal and the variance was not homogeneous, the Kruskal–Wallis test was applied. A p < 0.05 was considered statistically significant.

To reduce the variability due to the treatment intensity regimen, a cluster analysis was performed. As a result, patients were grouped according to the number of mean daily drugs, tablets, and DDs of medication received, and subsequently a descriptive analysis was performed according to the resulting groups of patients. Additionally, association analyses between the resulting groups of patients by treatment intensity and other patient variables were carried out. For the QOL variable, a cutoff point of ≥70% was used to classify patients into two categories depending on the achievement or not of QOL of ≥70% in VAS score or 0.7 in EQ index (which is an intermediate-high level). The cutoff points for deciding what is good or poor health-related QOL do not have a standard value among the scientific community because they depend on patient’s perceptions and values. In our study, the cutoff point was chosen based on the size of the resulting categories, particularly the category of those patients with poorer QOL. Patients with poorer QOL were those not achieving QOL of ≥70% in VAS score or 0.7 in EQ index. The Statistical Package for the Social Sciences (SPSS version 13) was used in data analysis.

Results
Socio-demographic characteristics
Data from 3462 questionnaires received between September and December 2007 were analyzed; 1983 questionnaires (out of 2005 received) were from RT patients from 45 Spanish provinces and 1479 questionnaires (out of 1487 received) were from LT patients from Spain (46 provinces) and Andorra.

Socio-demographic characteristics of RT and LT patients were comparable (see Table 1), except for mean time from first transplant, which was higher in RT patients (9.7 yr) compared with LT patients (6.4 yr).

Treatment characteristics
Medication characteristics are summarized in Table 2. The combination of two or more ISTs was more frequent in RT (82.3%) than in LT (43.2%) patients. More than half (52.4%) of RT patients and over one-third (36.7%) of LT patients reported one or more side effects caused by IST medication.

The mean number of daily tablets and drugs taken by RT (11.4 ± 4.7 tablets/d and 7.1 ± 3.3 -drugs/d) and LT patients (6.9 ± 4.5 tablets/d and 3.7 ± 2.5 drugs/d) was considerable. The total DD of medication received was above the mean medication intake in 25% of the RT (14 tablets of nine or more drugs each day) and LT (nine tablets of five or more drugs each day) patients. Transplant recipients received between 2 and 3 DDs of medication (mean 2.8 ± 0.9 for RT and 2.5 ± 0.9 for LT).

The cluster analyses carried out for reducing treatment regimen intensity variability (see Statistical analyses section) resulted in five groups of patients (groups A–E) for RT patients and four groups (groups a–d) for LT patients. RT and LT recipients were grouped in descending order by the treatment intensity regimen received, thus groups “A” (RT recipients) and “a” (LT recipients) included those receiving the highest-intensity regimens while groups “E” (RT) and “d” (LT) included those receiving the lowest-intensity regimens (see Table 3).

Adherence to IST and patient’s perceived barriers to adherence
In RT and LT patients, adherence to IST assessed as the number of times not taking IST (0.15 and
of LT patients answered their lifestyle was somehow limited (score ≥5).

Patient’s QOL

Most patients had no problems in the five QOL dimensions explored by using EQ-5D (see Fig. 1). Good QOL results were also obtained in the VAS scale (mean ± SD: 72.7 ± 18.3 for RT and 76.4 ± 17.6 for LT patients) and EQ index score (mean ± SD: 0.73 ± 0.16 for RT and LT patients). Moreover, when patients were inquired about their current health status compared with the previous year, a great majority of RT (90.6%) and LT (94.2%) patients said it was better or equal, and only 9.4% of RT patients and 5.9% of LT patients declared that their health status was worse.

Patient’s QOL and associated relevant factors

Association between treatment intensity and perception of adherence barriers and QOL is described
in Table 3. Except for controllable barriers in RT patients, less global barriers were perceived in patients with a small number of tablets and drugs administered daily; conversely, among those with superior treatment intensity regimens, the barriers perceived were higher. A better QOL (by VAS or EQ index) was associated with low-intensity treatment regimens as well.

As previously mentioned, poorer QOL was perceived in those patients not achieving QOL of ≥70% in VAS score or 0.7 in EQ index. According to this cutoff point, poorer QOL was perceived in subjects with female sex, aged 60 yr or more, with lower education levels, who were living in a reduced social network (alone or only with their partner), retired/homemakers, with high-intensity treatment regimens (more daily drugs, tablets, and DDs), who perceived that drug DDs difficult their QOL, who preferred to modify their DD to have a better adaptation to their family life than to their leisure, social or working schedule, and who suffered side effects. Overall, the proportion of transplant patients with poorer QOL (VAS Euro-Qol <70%) was higher in those receiving high-intensity treatment regimens compared with low-intensity treatment regimens (see Fig. 2).

### Discussion

Spain has reached the highest rate for donation and transplants per one million inhabitants worldwide (19). However, there is very little research related to IST adherence issues in RT patients in Spain (15, 16), and there are no data in LT patients. This is the first large-scale survey that explores patients’ perceptions, attitudes, and barriers to IST adherence and QOL in adult patients with RT and LT in Spain and provides useful data, especially as regards the population of LT patients for which data are scarce.

Overall, characteristics of RT and LT recipient populations analyzed were quite similar. Tacrolimus, mycophenolate, and steroids were the most common ISTs used in our RT patients, which is in agreement with the IST use we previously reported in a prospective evaluation of 2600 RT patients in Spain (20) and with usual practice.

RT patients in this study had a high adherence to treatment and are in line with previous studies in Spain (15). This adherence was higher to what is stated in international studies for RT (3) patients, and it could be explained by the fact that the sample was taken from patients affiliated to transplant associations, which indicates a possible selection bias. In addition, from the total transplant association affiliates, only those more motivated might have answered the questionnaire and, because it was a self-administered questionnaire, patients may have overestimated their adherence. Actually, self-reported adherence was also found to be high (88%) in a recent cross-sectional study by Gordon et al. (21) in 82 RT patients in United States. The regular control, support, and follow-up of the patient, which are characteristic of the Spanish HCS, may have contributed to this good adherence rates as well, similar to that shown in a

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**Table 3. Adherence barriers (ITBS) and QOL (EQ VAS and Mean EQ index) according to treatment intensity regimen**

<table>
<thead>
<tr>
<th>Treatment intensity regimen</th>
<th>RT groups</th>
<th>LT groups</th>
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<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>No. of daily drugs</td>
<td>10</td>
<td>6.5</td>
</tr>
<tr>
<td>No. of daily doses</td>
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<td>3</td>
</tr>
<tr>
<td>No. of daily tablets</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Adherence barriers on ITBS</td>
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<td></td>
</tr>
<tr>
<td>scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncontrollable barriers</td>
<td>11.6 (3.5)</td>
<td>11.2 (3.6)</td>
</tr>
<tr>
<td>Controllable barriers</td>
<td>4.5 (1.7)</td>
<td>4.6 (1.7)</td>
</tr>
<tr>
<td>Both barriers</td>
<td>16.1 (4.8)</td>
<td>15.8 (5.0)</td>
</tr>
<tr>
<td>QOL</td>
<td></td>
<td></td>
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<tr>
<td>EQ VAS</td>
<td>67.9 (18.5)</td>
<td>72.6 (17.8)</td>
</tr>
<tr>
<td>Mean EQ index</td>
<td>0.7 (0.2)</td>
<td>0.7 (0.1)</td>
</tr>
</tbody>
</table>

EQ, EuroQol; ITBS, Immunosuppressant Therapy Barrier Scale; LT, liver transplant; Qol, quality of life; RT, renal transplant; VAS, visual analog scale. All values are represented as mean (SD).

1 Patients were grouped in descending order (A–E, a–d groups) according to the treatment intensity regimen (number of mean daily drugs, tablets, and daily doses of medications) received (cluster analysis).

2 Kruskal–Wallis test.

3 Barriers that patients may perceive to be beyond their control.

4 Barriers that should be more within patients’ control with non-adherence occurring because of carelessness or deliberate intention not to adhere.
meta-analysis comparing US and European RT patients (22). Finally, the adolescent population, in which compliance rates are particularly low (23–25), is not included in our study, and this fact may have contributed to the high adherence rate reported here.

For LT recipients, IST adherence rate observed in our study was also high and consistent to that observed in the literature. In fact, evidence from most international studies (9–11, 14) suggests that medication adherence after liver transplantation is high and more favorable than that in RT patients.

One limitation of the study was that adherence was not confirmed by measuring the blood level of immunosuppressants. However, the questionnaire was anonymous, so we must assume that the patient’s answers were in line with their perception of reality. In fact, self-reported non-adherence has been found to be significantly related to non-adherence rates using more objective measures (26, 27). Nevertheless, non-adherence is hard to measure accurately, and highly standardized measurement methods and the determination of the validity of this assessment methods have been proposed by experts in a recent “consensus conference” (28). The analysis of data on IST adherence rates by the site or region was not considered appropriate in view of the differences observed in some patients regarding the site or region where they were followed and where they received their transplant. There was also a great variability in the time when the transplant was received. In addition, we assumed that there would be no important differences between sites because of the inherent characteristics of the Spanish HCS where control, support, and follow-up of the patient are very similar.

Adherence to treatment is influenced by several factors such as patient’s characteristics; disease; environment; number of daily tablets, drugs, and DDs of medication; side effects; and medications costs. These factors can act either as barriers or facilitators. In the study by Gordon et al. (21), a qualitative analysis of treatment adherence revealed that half of the patients reported experiencing at least one barrier to medication taking. According to our results, barriers to adherence are not very high, but ≥30% of RT and LT patients perceived “having to take the IST too many times
per day” or “having to take too many capsules or (tablets) of my IST medication at one time” as the main “uncontrollable” barrier to treatment adherence.

An important aspect for transplant efficacy is the increase observed both in life expectancy and in QOL. A very good health-related QOL is observed in this study, and only 9.4% of RT patients and 5.9% of LT patients declared that their health status was worse compared with previous year. However, one important finding was that the QOL perceived was lower with higher-intensity regimens: patients with QOL below 70% revealed some common characteristics: they were basically patients of female sex, aged 60 yr or more, with lower education levels, who were living in a reduced social network, they were not part of the active working population, and were taking ≥6 daily tablets and ≥2 DDs of medication. Most certainly, these patients had a number of comorbidities that contribute to the poorer QOL perceived. Nevertheless, they perceived that number of DDs of medication impaired their QOL and preferred to modify the number of DDs they receive to have a better adaptation to their family life.

From the study results, it can be concluded that adjustment of daily treatment intensity by using regimens that require less frequent dosing may be a good strategy to minimize barriers to adherence and improve QOL. These patients agreed that the reduction in the number of DDs of medication would be an improvement in the way how IST affects their life, especially if the evening dose was suppressed. Research in several chronic diseases has observed an inverse relationship between dosing frequency and medication adherence, with the highest adherence rates achieved with the simplest drug regimen (17). Simpler drug regimens can result in an improved health-related QOL and are preferred by patients than more complex regimens (8, 29). Furthermore, drug regimen complexity and dosing frequency have been recognized as barriers to adherence among transplant patients in the literature (30). A prospective multicenter study in 278 RT patients demonstrated that the probability to be treatment adherent was twofold superior with once-daily dosing compared with multidose regimens (31). In addition, the analysis of adherence to IST performed in 507 transplanted patients observed that the adherence rate was significantly lower (p < 0.001) for the evening than the morning dose (32). In fact, the simplification of therapy strategies, for example in the number of prescribed medications and in the dosing frequency, is one of the measures to reduce no adherence recommended in the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines recently published (2).

Newer immunosuppressive agents, particularly once-daily medications and long-acting antibody preparations, offer convenience and monitoring that might improve adherence rates among transplant patients and would substantially reduce the number of acute rejection episodes and graft failures (4). Nevertheless, other factors like patients characteristics and timing of medication intake should be taken into consideration to ensure medication adherence (33–35), and thus IS therapy needs to be individualized (36). In this particular, recent studies with new once-daily extended-release formulation of tacrolimus in stable LT recipients have shown to ensure appropriate and sustained drug blood levels with minimal dose adjustments in the short term (37, 38), leading to enhanced IST adherence (39).

In conclusion, this first large-scale survey in transplanted patients in Spain offers valuable results, particularly in LT patients where data are scarce. Results obtained in IST adherence and patient’s health-related QOL in this study are good, but offer a room for improvement. Adjustment of daily treatment intensity by using regimens that require less frequent dosing may be a good strategy to minimize barriers to adherence and improve QOL.

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Author contributions

Dr. Morales and Dr. Varo participated in the writing of the paper. Dr. Lázaro participated in research design and data analysis. All authors participated in the critical review of the article.

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