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Health-related quality of life and symptom experience in tacrolimus-based regimens after renal transplantation: a multicentre study

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Abstract Tacrolimus is increasingly used as a baseline immunosuppressant after renal transplantation. This multicentre study assessed health-related quality of life and symptom experience in renal transplant patients on tacrolimus-based therapy, using the SF-36 and Euroqol 5 dimensions (EQ-5D) and the 'modified transplant symptom occurrence and symptom distress scale', respectively. Symptoms of depression were assessed with the short form of the Beck Depression Inventory and physical activity with the Baecke questionnaire. Overall, 350 patients with a median post-transplant status of 16.7 months were enrolled. Results revealed that patients experienced lower SF-36 scores than the general population, except in terms of bodily pain. Univariate and multivariate analyses demonstrated that a higher degree of depressive symptoms and female gender were consistently related to a health status perceived as being worse and a higher rate of symptom experience. These findings are in accordance with previous quality-of-life reports that assessed patients under various immunosuppressive therapies. Therefore, interventions, including the screening and treatment for depression and the addressing of gender-specific issues, can enhance quality of life.

Keywords Quality of life · Renal transplantation · Immunosuppression · Side effects

Introduction

Quality of life is increasingly reported as being an important parameter in the assessment of the effectiveness of immunosuppressive regimens [11]. Quality-of-life assessments provide a detailed picture of the transplant patient's physical, psychological and social functioning. Moreover, specific aspects of quality of life, such as patients' perceived symptom experience associated with side effects of immunosuppressive drugs, allow one to have a better understanding of relevant issues for clinical transplant care [8].

A large number of quality-of-life studies in transplantation has been published since the introduction of cyclosporine (CsA) [11], resulting in a substantial amount of evidence. However, research that assesses quality of life in adult patients on tacrolimus-based regimens is less extensive [10, 17, 22, 29, 30, 34, 35, 41], though tacrolimus is increasingly used as standard immunosuppressive therapy after transplantation.

Moreover, findings are partly inconsistent, primarily due to issues related to the measurement of quality of life and differences among target populations. In addition, the majority of these studies were conducted in the early tacrolimus era. Optimisation of tacrolimus dosing, the application of more advanced combination therapies, and the lack of a formal assessment of transplant patients' perceived symptom experience associated with side effects of the tacrolimus-based regimens, demand a detailed assessment to be made of quality of life of this specific patient population. The aims of this study were, therefore, to assess comprehensively the health-related quality of life, including symptom experience, in renal transplant patients on tacrolimus-based maintenance immunosuppressive therapy; to explore the association between the type of combination therapy and quality of life; and to identify demographic and clinical variables related to quality of life.

Materials and methods

Study population

A convenience sample of 361 renal transplant recipients on a tacrolimus-based immunosuppressive regimen, who underwent operation and were followed-up at the University Hospitals of Leuven, the Academic Hospital Maastricht, and Cliniques Universitaires Saint-Luc, Brussels, were asked to participate in this study. Inclusion criteria were that patients should take tacrolimus, be 18 years of age or older at the time of inclusion, be literate, Dutch or French speaking, and provide written informed consent. Patient status had to be at least 6 months post-transplant and/or 6 months on a tacrolimus-based regimen, if they were converted from another regimen. Hence, only patients on maintenance immunosuppressive therapy were enrolled, since the immediate post-transplant period may distort the results. The quality of life during the first months after kidney transplantation may be negatively influenced by higher levels of immunosuppressants, resulting in increased symptom experience. Exclusion criteria for the study were re-transplantation or combined transplantation, e.g. kidney–pancreas. Eleven patients refused to participate, yielding a sample of 350 subjects.

The study was conducted from 1 December 1999 to 30 September 2000, and used two approaches to recruit eligible subjects. The majority of the patients were approached following a scheduled outpatient visit at their transplant clinic. Independent researchers, who were not members of the investigational team approached the patients and offered participation. They contacted 233 patients, and 230 patients (65.7%) were enrolled after having provided written informed consent. The patients received both oral and written instructions on how to complete the questionnaires. The researcher remained available to provide clarification if needed. Completeness of the instrument was checked by the researcher, and patients were asked to supply missing data if necessary. Furthermore, 128 patients who were followed-up by local nephrologists, were contacted by phone by the researchers of the tertiary care centres, and the questionnaires were subsequently mailed. Eight patients refused to participate. Hence, 120 patients (34.3%) returned the completed instruments, including the signed informed consent form, in a pre-addressed and stamped envelope. These two approaches were adopted because the analysis of the statistical power of a pilot study indicated that a sample size of approximately 350 patients was needed to obtain a power of approximately 80%. In order to obtain a sufficient sample size, two data collection methods were combined, as described above. The combining of the two recruitment strategies prevented a possible bias, namely that patients with a good clinical status be followed-up by their local nephrologists, while patients in a worse status be followed-up in a university hospital. Post-hoc analyses revealed, however, no significant differences in outcome between the two groups, which allowed pooling of the data.

The data collecting procedure required approximately 30 min. This study was approved by the local ethics committee of all three participating centres and has, therefore, been performed in accordance with international ethical standards. Informed consent entailed the use of medical records for the study.

Variables and measurement

Demographic and clinical variables were collected from the patients' medical records. For this study, we defined health-related quality of life as patients' subjective appraisal of their physical, psychological and social functioning. Hence, instruments assessing the physical, psychological and social domains of health were used. Symptom experience, referring to patients' perceptions of side effects of the immunosuppressive regimen was specifically assessed as a relevant quality-of-life parameter in this study [8]. Since it is argued that quality of life may also be associated with the degree of depressive symptoms and the level of physical activity, the influence of these two variables on the quality of life was also explored in this study. Established instruments, existing in Dutch and French, with adequate psychometric properties, were chosen for the measurement of the variables.

Medical outcome study—short-form 36

The medical outcome study—short-form 36 (SF-36) is a widely used generic instrument to measure patients' subjective health status along eight dimensions [42]. The SF-36 generates a score for each dimension, ranging from 0 to 100. Higher scores indicate a better health status. The SF-36 has been used extensively in various patient populations, allowing comparison of SF-36 scores between renal transplant patients, healthy individuals, and other chronically ill patient populations. Data on the SF-36 from the general population in the Netherlands are available according to gender and age [1], enabling comparison with data from this study.

Euroqol 5 dimensions

The Euroqol 5 dimensions (EQ-5D) self-classifier and EQ visual analogue scale (EQ VAS) [5] were used as further generic health status instruments. These tools are European standardised generic instruments for the measurement of patient-perceived health status. The EQ-5D self-classifier describes health states in five dimensions. A respondent's health state is constituted by a combination of the indicated levels from each of the five dimensions, generating a total of 243 possible health states. Each of the 243 health states corresponds to an index value that is computed on a particular set of weights collected from a representative sample of the general population. An index of 0 corresponds to death, while 1 refers to perfect health. In the absence of a valuation in the Belgian population, valuation data from the UK were used in this study to calculate the EQ-5D index [15].

Perceived health status is also assessed with a visual analogue scale (EQ VAS), ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

Modified transplant symptom occurrence and symptom distress scale

Symptom experience associated with side effects of immunosuppressive medication was measured with the 45-item version of the modified transplant symptom occurrence and symptom distress scale (MTSOSDS). This instrument was based on the 29-item version developed previously by our research group, comprising symptoms associated with CsA, corticosteroids and azathioprine [26], and was updated with symptoms relevant to side effects of tacrolimus and mycophenolate mofetil (MMF). The instrument measures symptom occurrence on a 5-point scale rating from 0 (never occurring) to 4 (always occurring); and symptom distress on the same scale, from 0 (not at all distressing) to 4 (extremely distressing). The versions for male/female patients differ on one item: impotence and painful and/or excessive menstrual flow, respectively. This instrument was translated into French and back into Dutch, by use of a standard translation protocol. The content validity of this instrument is based on an extensive literature review and has been tested by a panel of seven experts (data on file) [26].

Beck depression inventory

Symptoms of depression were measured with the 13-item version of the Beck depression inventory (BDI-13) [3]. Each item comprises four statements scored as a 4-point Likert-scale ranging from 0 to 3. Total scores thus range from 0 to 39, with patients being classified as not depressed (0–4), mildly depressed (5–7), moderately depressed (8–15), or severely depressed (16–39). The BDI is a sensitive screening instrument for depressive symptoms, but does not replace a psychiatric diagnosis of depression.

Baecke questionnaire

Habitual physical activity was assessed with the Baecke questionnaire [2], which comprises three dimensions: physical activity at work; sports during leisure time, and physical activity during leisure time, excluding sports. The instrument encompasses three open questions, eighteen 5-point rating items, and one dichotomous item. Based on the answers given by the patient, an index for the three dimensions can be calculated, by use of a predefined algorithm [2]. The indices for occupational activities, sports, and leisure range from 1 to 5. A higher index score refers to a higher level of activity.

Statistical analysis

The data were analysed by means of SPSS 9.0. Nominal level data were expressed in percentages. Medians and quartiles were calculated for continuous, non-normally distributed variables. In order to allow comparison with published data of previous quality of life research, we also computed means and standard deviations. To explore the impact of selected demographic and clinical variables (e.g. type of immunosuppressive regimen), as well as the impact of symptoms of depression and physical activities on perceived health status and symptom experience, we performed univariate and multivariate analyses. The Mann–Whitney U test was used for two-group comparisons, and the Kruskal–Wallis test for multiple-group comparisons. Multiple linear regression analysis (backward method) was used for multivariate statistics, after the assumptions underlying this statistical method had been checked. Table 1 describes the variables entered in this analysis. The level of significance was set at $P \leq 0.05$.

Differences in the SF-36 scores between renal transplant patients and the general Dutch population are expressed as standardised differences from the norm data. For each patient, the norm score of the corresponding age and gender category was subtracted from the patient's score and divided by the standard deviation from the norm data, which generated a standardised difference for that patient. The averaging of this difference over all patients resulted in a mean standardised difference. Values less than zero indicate that the perceived health of renal transplant patients is lower than the perceived health of the norm group, adjusted for age and gender.

Table 1 Independent variables used in the multiple linear regression analysis

Independent variables	Level of measurement
Transplantation centre	Categorical (nominal)
Gender	Categorical (nominal)
Age	Continuous
Marital state	Categorical (nominal)
Educational level	Categorical (ordinal)
Type of donor	Categorical (nominal)
Tacrolimus dose	Continuous
Tacrolimus blood level	Continuous
Steroid-containing or steroid-free regimen	Categorical (nominal)
Creatinine clearance	Continuous
Haemoglobin	Continuous
Number of rejections	Continuous
Converted from another regimen or not	Categorical (nominal)
Enough information about the reason of medication	Categorical (nominal)
Enough information about how to take the medication	Categorical (nominal)
Enough information about side effects of the medication	Categorical (nominal)
Beck depression inventory score	Continuous
Occupational activity index	Continuous
Sports activity index	Continuous
Leisure activity index	Continuous
Total activity index	Continuous
Symptom occurrence	Continuous
Symptom distress	Continuous
EQ-5D health index	Continuous
EQ VAS score	Continuous
Time after transplantation	Continuous

Table 2 Immunosuppressive regimens ($n = 350$)

Drug regimen	
Tacrolimus + steroids + MMF	33.7%
Tacrolimus + steroids	20.6%
Tacrolimus	20.0%
Tacrolimus + MMF	18.6%
Tacrolimus + steroids + azathioprine	6.0%
Tacrolimus + azathioprine	1.1%
Tacrolimus	
Patients on tacrolimus	100%
Median tacrolimus dose (mg/kg per day)	0.073 (IQR = 0.05)
Median time on tacrolimus (in months)	14.6 (IQR = 21.3); range 6–92.8
Steroids	
Patients on steroids	60.3%
Median steroid dose (prednisone equivalents mg/kg per day)	0.08 (IQR = 0.047)
Median time on steroids (in months)	13.8 (IQR = 31.6); range 0.8–185.4
Azathioprine	
Patients on azathioprine	7.1%
Median azathioprine dose (mg/kg per day)	0.98 (IQR = 0.449)
Median time on azathioprine (in months)	44.0 (IQR = 34.7); range 1.5–122.5
MMF	
Patients on MMF	52.3%
Median MMF dose (mg/kg per day)	15.38 (IQR = 8.12)
Median time on MMF (in months)	9.7 (IQR = 9.4); range 5.5–66.1

Symptom occurrence and symptom distress were measured at ordinary level. Therefore, ridit analysis, a sensitive statistical method for the analysis of ordinal data [6] was chosen. A ridit represents the Relative probability to an Identified Distribution. The ridit of a (sub)sample is always compared to the ridit of a chosen reference group. In this study, we obtained the reference group by using the frequency distribution of the whole sample over all items for the construction of a rank-order of the most often occurring and most distressing symptoms, and for comparisons of overall symptom occurrence and symptom distress between subgroups. For group comparisons at item level, the reference group was the sum of the frequency distribution of the sub-samples for each symptom. The ridit of a (sub)sample is the probability that a randomly selected individual from that group scores higher on the response variable than a randomly selected individual of the reference group. The calculation of ridits permits further parametric analysis (i.e. Students' *t*-test). A detailed description of this technique for the analysis of symptom experience in transplant patients has been reported previously [24, 26].

Results

Patient characteristics

Two hundred and nine male (59.7%) and 141 female (40.3%) renal transplant recipients were enrolled. The median age was 52 years (Q1 = 43; Q3 = 62, range 20–79). The majority of the patients were living in a stable relationship with their partner (74.5%). Median time after transplantation was 16.7 months (Q1 = 7.9; Q3 = 38.6). Table 2 describes the immunosuppressive regimens of the patients in this study. Of the patients, 34% were on a triple therapy with tacrolimus, corticosteroids and MMF, 20.6% were on dual therapy with tacrolimus and corticosteroids, and 20% were on tacrolimus monotherapy. Overall, 60.3% were on corticosteroids, 52% on MMF, and 7% on azathioprine.

Symptoms of depression and activity level

Median score on the BDI-13 was 2, ranging from 0 to 27. Accordingly, 72.3% of the patients were classified as showing no depressive symptoms, whereas 15.1%, 11.4% and 1.1% showed a mild, moderate and severe degree of depressive symptoms, respectively. Symptoms of depression were not associated with age, gender or marital status. The mean score on the occupational, sport and leisure activity index of the Baecke questionnaire was 2.67 (±0.64), 2.11 (±0.71), and 2.71 (±0.74), respectively, on a scale from 1 to 5. Two hundred and six patients (58.9%) were not employed at time of the study and were therefore removed from the analysis of the occupational activity index.

Perceived health status

The scores on the eight dimensions of the SF-36 ranged from 60.9 for general health to 78.8 for social functioning. Except for those of physical pain, the scores of the renal transplant patients on all dimensions were substantially lower than the age-corrected and gender-corrected norm data of the Dutch general population (Table 3). This difference is illustrated in Fig. 1, where the mean standardised differences between renal transplant recipients and the general population are compared.

Table 3 Perceived health status (SF-36), according to the respective tacrolimus-based regimens, gender and degree of depressive symptomatology ($n = 350$; *NS* not significant)

Parameter	Physical functioning	Role-physical functioning	Bodily pain	General health	Vitality	Social functioning	Role-emotional functioning	Mental health
Overall score	73.1 ± 24.0	61.8 ± 40.6	73.7 ± 24.8	60.9 ± 19.3	63.3 ± 19.7	78.8 ± 22.5	73.8 ± 38.2	71.6 ± 19.7
Norm data from the general population	82.1	75.3	73.4	69.2	69.1	84.2	82.4	76.9
Regimen								
Tacrolimus + steroids + MMF ($n = 118$)	72.8 ± 23.7	55.7 ± 43.2	73.3 ± 25.7	60.0 ± 19.4	62.8 ± 21.2	75.8 ± 23.6	73.4 ± 38.4	70.4 ± 19.0
Tacrolimus + steroids ($n = 72$)	72.8 ± 25.0	64.6 ± 40.0	73.4 ± 24.7	64.2 ± 18.0	60.7 ± 21.3	78.5 ± 19.8	66.7 ± 42.2	65.4 ± 22.6
Tacrolimus monotherapy ($n = 70$)	71.1 ± 23.6	60.7 ± 39.1	75.0 ± 23.0	60.4 ± 18.3	66.9 ± 15.2	81.3 ± 22.7	74.8 ± 37.4	77.6 ± 15.6
Tacrolimus + MMF ($n = 65$)	73.8 ± 25.1	70.0 ± 37.6	74.4 ± 25.2	60.1 ± 21.0	63.5 ± 20.7	81.2 ± 23.5	82.6 ± 34.4	73.1 ± 21.1
Tacrolimus + steroids + azathioprine ($n = 21$)	78.3 ± 20.9	61.9 ± 39.2	70.4 ± 27.9	58.9 ± 21.7	62.4 ± 17.7	78.6 ± 23.1	6.3 ± 35.7	74.3 ± 17.5
P	NS	NS	NS	NS	NS	NS	NS	0.014
Corticosteroids								
Steroid-containing regimen ($n = 211$)	73.4 ± 23.9	59.4 ± 41.7	73.0 ± 25.5	61.3 ± 19.2	62.0 ± 20.8	77.0 ± 22.3	70.6 ± 39.4	69.1 ± 20.2
Steroid-free regimen ($n = 139$)	72.7 ± 24.3	65.5 ± 38.7	74.8 ± 23.8	60.2 ± 19.5	65.3 ± 17.8	81.5 ± 22.7	78.6 ± 35.9	75.6 ± 18.3
P	NS	NS	NS	NS	NS	0.026	0.031	0.002
Gender								
Male ($n = 209$)	75.9 ± 23.8	64.7 ± 39.7	76.2 ± 24.4	61.0 ± 20.2	64.9 ± 19.9	80.1 ± 22.2	76.4 ± 36.9	73.3 ± 19.4
Female ($n = 141$)	68.9 ± 23.8	57.4 ± 41.7	70.0 ± 25.0	60.6 ± 18.0	61.0 ± 19.3	76.9 ± 23.0	70.0 ± 39.9	69.3 ± 20.0
P	0.001	NS	0.011	NS	0.045	NS	NS	0.05
Level of depressive symptomatology								
No depressive symptoms ($n = 253$)	79.1 ± 20.1	73.8 ± 35.2	78.9 ± 21.2	66.3 ± 16.9	70.2 ± 14.9	85.7 ± 17.2	84.6 ± 30.1	78.3 ± 14.1
Mild ($n = 53$)	57.4 ± 26.1	33.0 ± 36.3	65.0 ± 24.9	52.1 ± 16.2	50.6 ± 16.8	67.9 ± 24.1	54.7 ± 42.4	63.7 ± 17.9
Moderate or severe ($n = 44$)	57.2 ± 26.7	27.3 ± 38.1	54.3 ± 31.2	40.3 ± 18.1	39.1 ± 20.9	52.3 ± 23.1	34.8 ± 41.3	42.0 ± 20.5
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

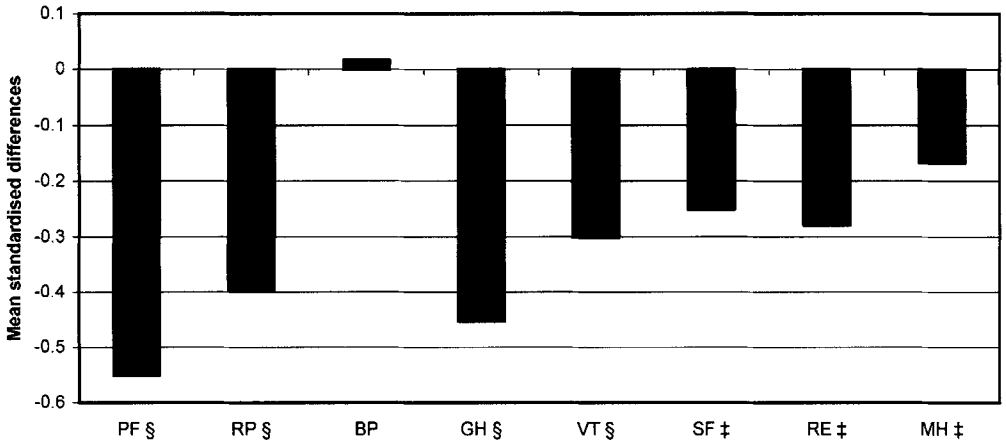

Fig. 1 Mean standardised differences between the SF-36 scores of 336 renal transplant recipients on a tacrolimus-based regimen and the Dutch general population (*PF* physical functioning, *RP* role-physical functioning, *BP* bodily pain, *GH* general health, *VT* vitality, *SF* social functioning, *RE* role-emotional functioning, *MH* mental health; ‡ $P < 0.01$; § $P < 0.001$)

Comparison of SF-36 scores among the various tacrolimus-based regimens revealed no significant differences, except for significantly better mental health ($\chi^2 = 12.6$; df = 4; $P = 0.014$) in patients on tacrolimus monotherapy (Table 3). Patients on a dual therapy of tacrolimus and steroids showed the lowest score for mental health. When steroid-free regimens were compared with steroid-containing regimens, it was found that patients on a tacrolimus-based regimen without steroids demonstrated significantly better social functioning (U = 12659; $P = 0.026$), better role emotional functioning (U = 12935; $P = 0.031$) and better general mental health (U = 11808; $P = 0.002$) than patients on steroids did.

Analysis by gender showed that male patients had significantly better physical functioning (U = 11632; $P = 0.001$), better functioning related to bodily pain (U = 12421; $P = 0.011$), greater vitality (U = 12877; $P = 0.045$), and better mental health (U = 12920; $P = 0.05$) than female patients.

The perceived health status of renal transplant patients was strongly associated with the degree of depressive symptoms. Significantly lower scores on all dimensions were found in patients with higher levels of depressive symptoms ($P < 0.001$) (Table 3). Note that the significant association between symptoms of depression and the respective dimensions of the SF-36 was also found at item level. Indeed, a significant negative correlation was found for all items of the BDI with the eight dimensions of the SF-36, except for sense of failure and guilt with physical functioning, role-physical functioning, and bodily pain; and for decreased appetite with physical pain.

Table 4 Perceived health status (EQ-5D self-classifier; $n = 350$)

Parameter	%
Mobility	
No problems with walking about	62.0%
Some problems with walking about	38.0%
Confined to bed	0.0%
Self-care	
No problems with self-care	92.9%
Some problems with washing or dressing	6.6%
Unable to wash or dress	0.6%
Usual activities	
No problems performing usual activities	68.9%
Some problems performing usual activities	27.1%
Unable to perform usual activities	4.0%
Pain/discomfort	
Neither pain nor discomfort	45.1%
Moderate	52.0%
Extreme	2.9%
Anxiety/depression	
Neither anxious nor depressed	69.4%
Moderately	26.9%
Extremely	3.7%

The EQ-5D self-classifier demonstrated a health status perceived as relatively good. The proportion of patients without any problems of mobility, self-care, usual activities and anxiety/depression ranged from 62% to 93% (Table 4). Yet, more than half of the patients reported moderate pain or discomfort. The median score on the EQ-5D index was 0.8 (Q1 = 0.69; Q3 = 1.0) and on the EQ VAS was 75 (Q1 = 70; Q3 = 85) (Table 5). The EQ-5D scores were not significantly influenced by the type of immunosuppressive regimen, the use of steroids or gender. Patients with mild or moderate/severe symptoms of depression, however, showed lower EQ-5D index scores ($\chi^2 = 82.4$; df = 2; $P < 0.001$) and EQ VAS scores ($\chi^2 = 96.6$; df = 2; $P < 0.001$) than patients without symptoms of depression. The clinical relevance of the EQ-5D index scores for the respective degrees of symptoms of depression (Table 5) can be illustrated by describing the corresponding health states [15]. An index score of 0.8, found in patients without symptoms of depression, is an evaluation that corresponds to no problems of mobility, self-care, usual activities, and anxiety/depression but with moderate pain or discomfort (i.e. health state 11121). An index score of 0.73 shows that the patient has no problems with mobility, self-care, and usual activities, yet perceives moderate pain or discomfort and moderate anxiety or depression (i.e. health state 11122). Finally, an index score of 0.52, observed in moderately/severely depressed patients, signifies moderate problems in all five dimensions (i.e. health state 22222). Obviously, a lower index score matches the description of a worse perceived health status.

To assess the association of demographic, clinical and regimen variables with perceived health status, we performed multiple linear regression analysis. With regard

Table 5 Perceived health status (EQ-5D index and EQ-VAS), according to the respective tacrolimus-based regimens, gender and degree of depressive symptomatology ($n = 350$; *NS* not significant)

Parameter	EQ-5D index	EQ VAS
Overall score	0.8 ($Q_1 = 0.69$; $Q_3 = 1.0$)	75 ($Q_1 = 70$; $Q_3 = 85$)
Regimen		
Tacrolimus + steroids + MMF ($n = 118$)	0.80 ($Q_1 = 0.73$; $Q_3 = 1.0$)	75 ($Q_1 = 69.75$; $Q_3 = 85$)
Tacrolimus + steroids ($n = 72$)	0.80 ($Q_1 = 0.69$; $Q_3 = 0.85$)	75 ($Q_1 = 70$; $Q_3 = 82.25$)
Tacrolimus monotherapy ($n = 70$)	0.80 ($Q_1 = 0.69$; $Q_3 = 0.91$)	79 ($Q_1 = 70$; $Q_3 = 0.85$)
Tacrolimus + MMF ($n = 65$)	0.80 ($Q_1 = 0.69$; $Q_3 = 1.0$)	75 ($Q_1 = 62.5$; $Q_3 = 81.5$)
Tacrolimus + steroids + azathioprine ($n = 21$)	0.73 ($Q_1 = 0.69$; $Q_3 = 0.80$)	76 ($Q_1 = 67.5$; $Q_3 = 86.5$)
P	NS	NS
Corticosteroids		
Steroid-containing regimen ($n = 211$)	0.80 ($Q_1 = 0.69$; $Q_3 = 1.0$)	75 ($Q_1 = 70$; $Q_3 = 85$)
Steroid-free regimen ($n = 139$)	0.80 ($Q_1 = 0.69$; $Q_3 = 1.0$)	79 ($Q_1 = 70$; $Q_3 = 80$)
P	NS	NS
Gender		
Male ($n = 209$)	0.80 ($Q_1 = 0.71$; $Q_3 = 1.0$)	80 ($Q_1 = 70$; $Q_3 = 89$)
Female ($n = 141$)	0.76 ($Q_1 = 0.69$; $Q_3 = 0.85$)	75 ($Q_1 = 70$; $Q_3 = 80$)
P	NS	NS
Level of depressive symptoms		
No depressive symptoms ($n = 253$)	0.8 ($Q_1 = 0.73$; $Q_3 = 1.0$)	80 ($Q_1 = 70$; $Q_3 = 90$)
Mild ($n = 53$)	0.73 ($Q_1 = 0.66$; $Q_3 = 0.81$)	70 ($Q_1 = 60$; $Q_3 = 75$)
Moderate or severe ($n = 44$)	0.52 ($Q_1 = 0.205$; $Q_3 = 0.73$)	54 ($Q_1 = 46.25$; $Q_3 = 69$)
P	< 0.001	< 0.001

to the SF-36, only for general health, vitality and mental health were the assumptions for performing this analysis fulfilled, i.e. residuals that are normally distributed, that have constant variance, and that are independent of each other. We therefore preferred to limit the multivariate regression analysis to the EQ VAS. A better perceived health was explained by fewer depressive symptoms ($\beta = -1.667$; SE = 0.183; $P < 0.001$), higher occupational activity index ($\beta = 1.573$; SE = 0.438; $P < 0.001$), higher sports-activity index ($\beta = 3.137$; SE = 0.885; $P < 0.001$), and less symptom occurrence ($\beta = -31.601$; SE = 7.901; $P < 0.001$) (constant = 88.271; SE = 4.088; $P < 0.001$). This model explained 46% of the variance of perceived health status.

Symptom experience

Overall scores

There were significant differences in the overall ridits of symptom occurrence and symptom distress between the tacrolimus-based regimens (Table 6). Dual therapy with tacrolimus and steroids showed the highest ridit for symptom occurrence, whereas tacrolimus monotherapy resulted in a significantly lower symptom occurrence ($t = 67.69$; $P < 0.001$). For symptom distress, triple therapy of tacrolimus, steroids and azathioprine produced the highest score, while the lowest score was observed with a dual therapy of tacrolimus and MMF ($t = -37.28$; $P < 0.001$). Stratification by steroid-containing and steroid-free regimens showed a significantly higher symptom occurrence ($t = -82.4$; $P < 0.001$) and symptom distress score ($t = -121$; $P < 0.001$) in patients on steroids. Symptom occurrence ($t = -368.9$; $P < 0.001$) and symptom distress ($t = -205.1$; $P < 0.001$) were significantly higher in female renal transplant recipients. Also, in patients with a higher degree of depressive symptoms, significantly higher symptom occurrence ($\chi^2 = 87.87$; df = 2; $P < 0.001$) and symptom distress ($\chi^2 = 73.94$; df = 2; $P < 0.001$) was observed.

Item scores

Analysis on item level resulted in a rank order of the most-often occurring and most distressing symptoms for male and female patients, respectively. Fatigue occurred most frequently, both in men and women (Table 7). Furthermore, the top-ten list of symptoms that occurred in both male and female patients included increased appetite, trembling hands, eyesight problems, sleeplessness, pain in the joints, and brittle skin. The most distressing symptoms for men were muscular weakness, and for women, hair loss. Symptoms that were distressing for both genders were muscular weakness, light sensitivity, trembling hands, pain in the joints, anxiety, pain in the back, and sleeplessness.

Although tacrolimus-based regimens with steroids resulted in higher overall symptom occurrence and symptom distress, analysis at item level provides a more detailed picture (Table 8). Of 45 symptoms monitored, 18 occurred significantly more frequently in tacrolimus-based regimens that contained steroids, whereas 20 symptoms occurred more often in steroid-free tacrolimus therapies. For seven symptoms, no statistically significant difference was found. Twenty-one symptoms were more distressing in regimens with steroids, six in steroid-free regimens, and for 18 symptoms no difference was observed.

Multiple linear regression analysis revealed that a higher level of symptom occurrence is explained by

Table 6 Symptom occurrence and symptom distress, according to the respective tacrolimus-based regimens, gender and degree of depressive symptomatology ($n = 350$)

Parameter	Symptom occurrence ridit	Symptom distress ridit
Regimen		
Tacrolimus + steroids + MMF ($n = 118$)	0.498	0.511
Tacrolimus + steroids ($n = 72$)	0.509	0.510
Tacrolimus monotherapy ($n = 70$)	0.494	0.491
Tacrolimus + MMF ($n = 65$)	0.498	0.475
Tacrolimus + steroids + azathioprine ($n = 21$)	0.500	0.513
P	< 0.001	< 0.001
Corticosteroids		
Steroid-containing regimen ($n = 211$)	0.503	0.511
Steroid-free regimen ($n = 139$)	0.496	0.483
P	< 0.001	< 0.001
Gender		
Male ($n = 209$)	0.486	0.480
Female ($n = 141$)	0.520	0.526
P	< 0.001	< 0.001
Level of depressive symptomatology		
No depressive symptoms ($n = 253$)	0.471	0.430
Mild ($n = 53$)	0.548	0.555
Moderate or severe ($n = 44$)	0.607	0.638
P	< 0.001	< 0.001

Table 7 Rank order of most occurring and distressing symptoms ($n = 350$)

Symptom occurrence	
Men ($n = 209$)	Women ($n = 141$)
1. Fatigue	1. Fatigue
2. Increased appetite	2. Sleeplessness
3. Trembling hands	3. Increased appetite
4. Difficulties with concentration	4. Brittle skin
5. Difficulty seeing well	5. Bruises
6. Sleeplessness	6. Difficulty seeing well
7. Mood swings	7. Trembling hands
8. Pain in joints	8. Pain in joints
9. Muscle weakness	9. Back pain
10. Brittle skin	10. Hair loss
Symptom distress	
Men ($n = 209$)	Women ($n = 141$)
1. Muscle weakness	1. Hair loss
2. Impotence	2. Pain in joints
3. Sensitive to light	3. Painful menstrual flow
4. Trembling hands	4. Sensitive to light
5. Pain in joints	5. Sleeplessness
6. Difficulty seeing well	6. Back pain
7. Anxiety	7. Increased hair growth
8. Brittle skin	8. Muscle weakness
9. Back pain	9. Anxiety
10. Sleeplessness	10. Trembling hands

female gender ($\beta = 0.032$; SE = 0.008; $P < 0.001$), higher sports-activity index ($\beta = 0.011$; SE = 0.006; $P = 0.062$), a lower health status measured with the EQ VAS ($\beta = -0.001$; SE = 0.000; $P < 0.001$) and more depressive symptoms ($\beta = 0.01$; SE = 0.001; $P < 0.001$) (constant = 0.535; SE = 0.031; $P < 0.001$). A higher level of symptom distress could be explained by female gender ($\beta = 0.052$; SE = 0.017; $P = 0.002$), lower age ($\beta = -0.002$; SE = 0.001; $P = 0.002$), more depressive symptoms ($\beta = 0.015$; SE = 0.003; $P < 0.001$) and a lower health status ($\beta = -0.002$; SE = 0.001; $P < 0.017$) (constant = 0.625; SE = 0.073; $P < 0.001$). These models explained 40% of the variance of symptom occurrence and 27% of symptom distress.

Discussion

This is the largest study to date that assessed health-related quality of life in a sample of renal transplant recipients on tacrolimus-based regimens. The methods applied to assess health-related quality of life in this study are congruent with current standards for quality-of-life assessment in transplantation [43], as the assessed physical, psychological and social domains of health are known to be strongly related to patients' overall quality of life [37, 42]. Moreover, this study expands earlier quality-of-life research in this field by also including a formal assessment of patients' symptom experience, a previously understudied area [8].

As expected, this study indicates that renal transplant recipients perceive their health status as being substantially lower than that of the general population. This is consistent with previous findings in renal transplant patients that are receiving other immunosuppressive regimens [4, 20, 23, 35, 38] and with other chronically ill patient populations [33]. This indicates that it is not the tacrolimus-based regimen as such that is responsible for the perception of low health status, it is the overall condition of the patient. More specifically, physical functioning, general health and role-physical functioning seems to be consistently lower in renal transplant patients [20, 38]. Scores on bodily pain were similar to those of the general population [20, 38]. Nevertheless, renal transplant patients tend to perceive their health status as being higher than dialysis patients [4, 18].

Results obtained with the EQ-5D in our sample could not be compared with those of the general population, since no data from the Belgian or Dutch population are available yet. It is not known whether the EQ-5D would reveal a similar difference in perceived health status between patients and the general population, as the SF-36 did. The EQ-5D, an instrument developed initially for economic evaluations, seems to show less sensitivity in discriminating among degrees of health status than does the SF-36. Since this is the first study in renal transplantation that evaluated quality of life using the EQ-5D, no comparisons can be made.

Exploration of differences in health-related quality of life among various tacrolimus-based regimens suggested in the univariate analyses that patients on tacrolimus monotherapy had significantly better scores. Note, however, that the descriptive design of this study and the use of a convenience sample are methodological limitations. Moreover, since there was a lack of randomisation, differences in quality of life among the treatment groups could be due to the various immunosuppressive strategies used in the participating transplant centres or due to clinical differences among patient groups. Patients receiving monotherapy, for instance, could potentially have an overall better clinical condition, resulting in a better health status. Furthermore, multivariate analyses did not confirm the differences in univariate analyses, which suggested that other factors influence the quality of life. This demonstrates the value of the multivariate statistics, because univariate analyses do not consider possible interactions or co-variation between different variables.

Findings regarding symptom experience confirm clinical experience. More specifically, the symptom profile associated with side effects of the tacrolimus-based regimens shows fewer cosmetic side effects than have been found in patients on CsA-based regimens [25, 36]. Cyclosporine A is associated with hypertrichosis, gingival hyperplasia and abnormal facial bone growth. The most frequently occurring and most distressing

Table 8 Comparison of symptom occurrence and symptom distress between renal transplant patients on a tacrolimus-based regimen containing steroids and a steroid-free regimen (*NS* not significant)

Symptom	Symptom occurrence			Symptom distress		
	With steroids ($n=211$)	Without steroids ($n=139$)	*P*	With steroids ($n=211$)	Without steroids ($n=139$)	*P*
Pimples	0.480	0.531	<0.001	0.498	0.503	NS
Listlessness	0.505	0.492	<0.01	0.503	0.495	NS
Difficulty seeing well	0.501	0.498	NS	0.485	0.524	<0.001
Fever	0.504	0.493	<0.001	0.501	0.498	NS
Depressive state	0.513	0.480	<0.001	0.501	0.498	NS
Increased appetite	0.528	0.457	<0.001	0.523	0.461	<0.001
Feelings of warmth in hands and feet	0.486	0.521	<0.001	0.536	0.454	<0.001
Impotence/painful or excessive menstrual flow	0.500	0.500	NS	0.477	0.534	<0.001
Growth of gums	0.487	0.520	<0.001	0.439	0.559	<0.001
Swollen ankles	0.478	0.533	<0.001	0.498	0.503	NS
Diarrhoea	0.479	0.531	<0.001	0.512	0.485	<0.01
Moon face	0.551	0.423	<0.001	0.507	0.472	<0.05
Decreased interest in sex	0.484	0.524	<0.001	0.498	0.503	NS
Being stressed	0.500	0.500	NS	0.499	0.502	NS
Back pain	0.510	0.485	<0.001	0.535	0.445	<0.001
Hair loss	0.523	0.465	<0.001	0.532	0.442	<0.001
Upset stomach and/or nausea	0.495	0.508	<0.01	0.538	0.450	<0.001
Anxiety	0.525	0.462	<0.001	0.499	0.503	NS
Changed body appearance	0.496	0.506	<0.05	0.534	0.454	<0.001
Mood swings	0.504	0.494	<0.05	0.532	0.452	<0.001
Cough	0.496	0.506	<0.05	0.500	0.500	NS
Headache	0.492	0.512	<0.001	0.532	0.456	<0.001
Changed facial features	0.524	0.464	<0.001	0.505	0.489	NS
Brittle skin	0.533	0.451	<0.001	0.502	0.496	NS
Vomiting	0.499	0.502	NS	0.528	0.460	<0.05
Concentration difficulties	0.512	0.482	<0.001	0.500	0.500	NS
Warts	0.491	0.514	<0.001	0.592	0.391	<0.001
Increased hair growth	0.520	0.469	<0.001	0.493	0.516	NS
Difficulties with sleeping	0.490	0.515	<0.001	0.475	0.535	<0.001
Sensitivity to light	0.493	0.511	<0.001	0.498	0.503	NS
Muscle weakness	0.522	0.467	<0.001	0.526	0.456	<0.001
Changed sense of taste	0.498	0.502	NS	0.523	0.466	NS
Hallucinations	0.489	0.517	<0.001	0.515	0.488	NS
Trembling hands	0.556	0.415	<0.001	0.519	0.459	<0.001
Poor appetite	0.489	0.516	<0.001	0.533	0.462	<0.001
Fatigue	0.494	0.508	<0.001	0.517	0.476	<0.001
Bruises	0.560	0.410	<0.001	0.537	0.409	<0.001
Tingling in hands and feet	0.491	0.514	<0.001	0.523	0.470	<0.001
Pains in joints	0.465	0.553	<0.001	0.480	0.523	<0.001
Burning sensation when voiding	0.500	0.499	NS	0.555	0.416	<0.01
Skin rash	0.503	0.496	NS	0.476	0.539	<0.001
Abdominal pain	0.479	0.532	<0.001	0.494	0.507	NS
Muscle cramps	0.506	0.491	<0.001	0.512	0.481	<0.001
Nightmares	0.504	0.493	<0.01	0.504	0.493	NS
Mouth infections	0.495	0.508	<0.001	0.526	0.465	<0.01

symptoms perceived by patients on CsA-based regimens were bruises, fragile skin, increased hair growth, moon face, changed bodily appearance, and acne [25, 36]. The high proportion of patients on a steroid-free tacrolimus-based regimen in our sample (40%) may also have contributed to the low prevalence of cosmetic symptoms.

Discrepancies between our list of side effects and those typically monitored by clinicians also show the relevance of assessing side effects from the patients' perspective. The ranking of most-often occurring and most distressing symptoms provides clinicians with the opportunity to inform patients which symptoms they are likely to perceive while receiving a tacrolimus-based regimen.

Comparison of symptom experience between steroid containing and steroid-free regimens revealed that side effects, such as brittle skin, bruises, increased hair

growth, muscle weakness, and moon face were, not surprisingly, significantly higher in steroid-containing regimens. Symptoms that may be attributed to tacrolimus and MMF, such as diarrhoea, upset stomach and/or nausea, poor appetite, abdominal pain, vomiting, mouth infections, tremor, headache, and paraesthesia, occurred more often in steroid-free regimens.

Depressive symptoms

Symptoms of depression emerged as a significant problem in this sample. They have been found to be more prevalent in transplant recipients than in the general population. The incidence of symptoms of depression (mild to severe) in this sample was 27.7%. This is in accordance with previous findings in renal transplant patients under various immunosuppressive regimens [26, 32]. The incidence in the general population has been found to be 15.9% [26]. It is important to bear in mind that these rates were determined by use of the sensitive BDI instrument, which correlates with, but in no way replaces, a psychiatric diagnosis of depression.

Symptoms of depression were found to be an important mediator in health-related quality of life and symptom experience in our study, as even a minor degree of depressive symptoms was associated with a lower level of quality of life. Moreover, it has been argued that depression is associated with increased morbidity and mortality [12, 31], and a substantially higher risk for medication non-compliance [13].

These findings underline the importance of careful evaluation for symptoms of depression during the post-transplant course. A thorough assessment of depressive disorder, using a structured diagnostic interview, is not feasible in daily clinical practice, because it is time consuming and requires specific expertise. Yet, a systematic screening for depressive symptoms by means of self-report instruments, once or twice a year during the post-transplant course, is valuable. We advise the use of well-validated instruments that comprise very few somatic items, because somatic complaints due to the medical problem may confound the interpretation of the screening results (i.e. false positives). Several tools that meet these requirements are available, e.g. BDI-13, hospital anxiety and depression scale (HADS) and Center for Epidemiologic Studies depression (CES-D) scale. These instruments can be easily and rapidly applied in chronically ill patient populations [14].

Systematic screening is only useful if patients with positive screening results are referred to specialised services for further psychiatric evaluation. If the diagnosis of depressive disorder is made, targeted interventions, such as pharmacological and psychotherapeutic treatment, can be initiated. The choice of anti-depressive agents in transplant patients requires, however, careful consideration. Several case studies showed an interaction of immunosuppressive medication with antidepressants having selective serotonin re-uptake inhibitory properties. For instance, interactions between tacrolimus and nefazodone [7, 28], and between CsA and fluoxetine [19], fluvoxamine [40], nefazodone [40, 45], sertraline [44], and bupropion [21] have been described, inhibiting metabolisation of the immunosuppressant, resulting in higher blood levels. Also the use of St John's wort, a herbal medicine that is considered as a folk remedy for depression, has been found to reduce the therapeutic activity of CsA, endangering the success of organ transplantation [16]. This underlines the importance of thorough assessment of medication used, including herbal medicines.

In this study, we used the BDI-13 for the evaluation of depressive symptoms, because this instrument is widely used in transplant and other non-psychiatric populations. Previous studies revealed high internal consistency reliability and good validity [3, 9]. Yet, not much is known about the validity of the short form of the BDI for use in renal transplant patients. For instance, information on the factor structure of the BDI-13 in this patient population is lacking. Secondary data analysis and factor analysis on data of this study may, however, provide additional information on validity and reliability of this instrument for renal transplant recipients.

Gender

Both univariate and multivariate analyses revealed that female transplant recipients perceived their health status as being significantly lower, with a higher level of symptoms than the male recipients. This is consistent with findings from transplant and other patient populations [24]. Gender-specific approaches in transplant patient management seem therefore indicated. Special attention to female patients dealing with side effects of the immunosuppressive regimen is therefore crucial.

Some of the dimensions of the SF-36 did not reveal significant differences. This could be explained by the relatively high variability in scores for those particular dimensions, e.g. role-physical functioning and role-emotional functioning. Variability is an important parameter for determining statistical significance. High variability decreases the likelihood for statistical significance. Overall, variability in the dimensions of role-physical functioning and role-emotional functioning was almost double the variability of other SF-36 dimensions.

Habitual physical activities

The scores on the Baecke questionnaire correspond with findings from other studies in renal transplant patients [27, 39]. Hence, the level of physical activity of this

sample can be considered as being lower than that of healthy controls [27]. Multivariate models revealed that a higher level of sports activities was associated with higher perceived health status, more symptom occurrence and less symptom distress. The positive relationship between sports activities and the occurrence of symptoms was surprising. Also the occupational activity level was positively related to perceived health. This indicates that habitual physical activity is a relevant issue in renal transplant patients' quality of life and should, therefore, be scrutinised in further research.

Conclusion

In this multicentre study, we assessed the health-related quality of life and symptom experience of adult renal transplant patients on tacrolimus-based therapy. We demonstrated that renal transplant patients perceived their health status as being lower than that of the general population. This is commonly observed in renal transplant patients under various immunosuppressive regimens. Quality of life and symptom experience seem to be predominantly determined by the level of depressive symptoms and gender. No firm associations with various tacrolimus-based regimens were found. This is valuable information for the clinical management of renal transplant patients under this specific regimen. In particular, understanding patients' perception of side effects related to the immunosuppressive regimen is essential for accurate patient education and for the development of strategies to enhance quality of life.

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