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Health-related Quality of Life and Fatigue in Liver Transplant Recipients Receiving Tacrolimus Versus Sirolimus-based Immunosuppression: Results From a Randomized Trial

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Background. The impact of different immunosuppression regimes on the health-related quality of life (HRQoL) and the severity of fatigue in liver transplant recipients is largely unknown. We investigated the impact of a sirolimus-based regimen compared with a tacrolimus (TAC)-based regimen on the HRQoL and the severity of fatigue. **Methods.** In this multicenter, open-label, randomized, controlled trial, 196 patients were randomized 90 d after transplantation to (1) once daily normal-dose TAC or (2) once daily combination therapy of low-dose sirolimus and TAC. HRQoL was measured with the EQ-5D-5L questionnaire, the EQ–visual analog scale, and the severity of fatigue questionnaire Fatigue Severity Score (FSS). The EQ-5D-5L scores were translated to societal values. We examined the HRQoL and the FSS over the course of the study by fitting generalized mixed-effect models. **Results.** Baseline questionnaires were available for 87.7% (172/196) of the patients. Overall, patients reported the least problems in the states of self-care and anxiety/depression and the most problems in the states of usual activities and pain/discomfort. No significant differences in HrQol and FSS were seen between the 2 groups. During follow-up, the societal values of the EQ-5D-5L health states and the patient's self-rated EQ–visual analog scale score were a little lower than those of the general Dutch population in both study arms. **Conclusions.** The HRQoL and FSS were comparable in the 36 mo after liver transplantation in both study groups. The HRQoL of all transplanted patients approximated that of the general Dutch population, suggesting little to no residual symptoms in the long term after transplantation.

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INTRODUCTION

Liver transplantation (LT) is a lifesaving therapy, and life expectancy after LT is increasing with 5-y survival rates of over 70%.[1] After an LT, patients experience a rapid improvement in their physical and mental condition. Important factors contributing to the well-being of an LT recipient in the long term are the health-related quality of life (HRQoL) and the severity of fatigue.

Various studies describe a substantial benefit in the HRQoL after LT.[2] Quality of life is a multidimensional construct reflecting the physical, mental, or psychological, and social dimensions of health.[3] A review by Yang et al showed that the HRQoL and general health perception of LT recipients improved to a similar level as the general population, except for physical functioning.[4]

Fatigue in patients after LT is a major issue in the long term. van Ginneken et al reported high rates of fatigue in LT recipients, and Lin et al showed that fatigue is strongly associated with insomnia, anxiety, and depression.[5,6] Furthermore, several studies showed higher fatigue scores reported by LT recipients than by the general population.[7,8]

The impact of different immunosuppression regimes on the HRQoL and the severity of fatigue in LT recipients is largely unknown. Benzing et al investigated the impact of 3 different immunosuppression regimes on the HRQoL following orthotopic LT.[9] In their observational study, in 275 LT recipients, they compared calcineurin inhibitors, mTOR inhibitors, and mTOR inhibitors combined with calcineurin inhibitors. The authors conclude that mTOR inhibitor–based regimens have beneficial effects on HRQoL, especially after an early conversion. A major drawback of this study was the retrospective nature of this study. Therefore, a prospective, randomized trial comparing the combination of low-dose sirolimus (SRL) and extended-release tacrolimus (TAC) to normal-dose extended-release TAC on the HRQoL and the severity of fatigue could be instrumental to evaluate this presumed beneficial effect of mTOR inhibitor–based regimens on HRQoL after LT.

MATERIALS AND METHODS

Study Design and Participants

An extensive description of the LOLIII study design has been published previously.[10] In brief, the LOLIII study randomized patients 90 d after transplantation in a 1:1 ratio to (1) once daily normal-dose TAC with target trough levels 5 to 10 μg/L (control group) or (2) once daily combination therapy of SRL and low-dose TAC with target trough levels 3 to 5 μg/L for both SRL and TAC (interventional group). During the 3-y follow-up, a switch in immunosuppressive therapy occurred in 48.9% (48/98) of the patients in the control group and in 44.9% (44/98) of the patients in the interventional group. In the control group, the main reason for the switch in immunosuppressive therapy was deterioration of the kidney function (43/48, 89.6%).[10] In the interventional group, multiple reasons for switching applied. The main reasons for a switch were side effects of SRL and/or preference of the treating physician with another immunosuppressive agent in the case of deterioration of kidney function (29/44, 65.9%). The side effects consisted mainly of pancytopenia, malaise, and skin problems.[10] The majority of the LT recipients were switched within the first year after transplantation (69/92, 75%) to mycophenolic acid.

The study was performed at 3 centers in The Netherlands: Erasmus University Medical Center Rotterdam, University Medical Center Groningen, and Leiden University Medical Center. The study was approved by the Ethical Committee of the Erasmus University Medical Center (MEC-2010-247), registered in the EudraCT database (EudraCT: 2009-017843-32), and conducted in accordance with the principles of the Declaration of Helsinki. All participants gave written informed consent before any study-related activity. The inclusion period ran from February 2011 to August 2018.

Patient-reported Outcomes

The evaluation of HRQoL and the severity of fatigue comprised a secondary objective of the LOLIII study. The LOLIII study was initially designed to investigate whether the combination of low-dose SRL and extended-release TAC compared with normal-dose extended-release TAC results in a difference in the renal function and comparable rates of rejection, graft survival, and patient survival at 36 mo after transplantation.

HRQoL and Severity of Fatigue Assessments

HRQoL was assessed with the validated Dutch version of the EQ-5D-5L questionnaire (a generic HRQoL instrument) and the severity of fatigue questionnaire (a domain-specific HRQoL instrument), the latter using the Fatigue Severity Score (FSS). The questionnaires were distributed at the moment of randomization and every year during the study until the end of follow-up, death, or withdrawal due to any reason. At the start of the study, the SF-36 questionnaire (a generic HRQoL instrument) was used for the assessment of the HRQoL, and in November 2011, a switch to the EQ-5D-5L questionnaire was made. Scores of the SF-36 questionnaire of 13 LT recipients were dropped.

The EQ-5D-5L questionnaire is based on a descriptive system that defines health in terms of 5 states: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[11] Each dimension has 5 response categories corresponding to no problems, slight problems, moderate problems, severe problems, and extreme problems. EQ-5D-5L scores were transformed into societal values based on the Dutch tariff for the EQ-5D-5L established by Versteegh et al.[12]

In the EQ-5D-5L questionnaire, the respondents' overall health (patient's self-rated HRQoL scores) on the day of the interview was rated on a 0 to 100 hash-marked, vertical visual analog scale (EQ-VAS). The threshold for the minimally important difference (MID), indicating a clinically meaningful improvement, in the EQ-VAS score, was defined as ≥7 points.[13]

The severity of FSS is a 9-question, self-administered questionnaire with answers ranging from 1 ("strongly disagree") to 7 ("strongly agree").[14] For each patient, the mean question score ranged from 1 ("no signs of fatigue") to 7 ("most disabling fatigue"). Based on a

study by van den Berg-Emons et al, patients were classified as "severely fatigued" with FSS scores ≥2 SDs above the mean score for healthy individuals (FSS ≥ 5.1). Patients were classified as "fatigued" for FSS scores ≥1 SD above the mean score for healthy individuals (4.0 ≥ FSS < 5.1).[15]

Data Collection

Variables collected included recipient socio-demographic, clinical, and transplantation parameters, the HRQoL and FSS and trough levels of SRL, and extended-release TAC.

Statistical Analysis

The HRQoL analysis included all patients within the LOLIII study who responded to at least 1 questionnaire, according to the intention-to-treat (ITT) principle. The EQ-5D-5L and FSS questionnaire included in the analysis missed <5% based on the total number of measurements across all patients and questions. The missing data were considered as missing completely at random.

Variables were described using counts (%) for nominal and ordinal variables and mean (SD) or median (interquartile range [IQR]) for continuous variables, depending on the shape of the distribution.

Three generalized linear mixed-effect models were fitted to examine the HRQoL (EQ-VAS and the societal values of the EQ-5D-5L) and the severity of fatigue over the course of the study. The models included covariates shown or suggested to be relevant: visit number, study group, TAC trough concentrations, kidney function, hemoglobin, recipient age and sex, primary disease, the usage of antihypertensive and antidiabetic drugs, and the usage of corticosteroids, as well as the interaction between visit and the study group. Additionally, the model examining the severity of fatigue included the covariate usage of mycophenolate mofetil (MMF). Participant-specific random intercepts were included to account for correlation among repeated measurements nested within each participant. Natural cubic splines were used to model the potentially nonlinear trajectories of the EQ-VAS, societal values of the EQ-5D-5L, and severity of fatigue over time. The need for these splines was evaluated using likelihood-ratio tests. Splines provide a convenient nonparametric way to flexibly model (potentially) nonlinear associations in regression models. Instead of using 1 polynomial (eg, a quadratic or cubic function) that spreads over the whole range of the covariate, splines use a set of several polynomial functions that are defined over smaller intervals. This allows the resulting fit to be more flexible than when using a single polynomial. To visualize the estimated associations, the expected HRQoL and severity of fatigue across the course of the study were calculated while fixing the values of all other covariates to the median or reference category.

Data were approached in an ITT and per protocol (PP) analysis. Patients with protocol violations in immunosuppressive therapy, retransplantation, or death were excluded from the PP analysis. Differences in the proportion of responses by level of severity for EQ-5D-5L dimensions were tested using the chi-square test. A P value of <0.05 was considered statistically significant. All data were collected in the Dutch Organ Transplantation Registry (NOTR), and analysis was performed using R software (version 3.6.2).[16]

RESULTS

Patient and Treatment Characteristics

A total of 196 patients were included and randomized in the LOLIII study. In total, 157 (80.1%) patients responded to the EQ-5D-5L baseline questionnaire, 78 (79.6%) patients in the control group and 79 (80.6%) patients in the interventional group. A total of 172 (87.7%) patients responded to the baseline severity of FSS, 87 (88.8%) in the control group and 85 (86.7%) in the interventional group. The response rate decreased during follow-up to a minimum of 66.3% on the 3-y questionnaire (Figure 1).

Table 1 shows the baseline characteristics of the ITT population. No relevant differences in any of the baseline characteristics between the 2 groups in either questionnaire were shown.

HRQoL Outcomes

Figure 2 shows the proportion of responses by the level of severity for EQ-5D-5L dimensions during the study period for the ITT population. Overall, patients reported the least problems in the states of self-care and anxiety/depression and the most problems in the states of usual activities and pain/discomfort. No evidence for significant differences between the study groups in any of the 5 states was found. Patients reported significantly more often "no problems" in the states of usual activities (P = 0.04) and pain/discomfort (P = 0.02) at year 3 compared with the moment of randomization in both study groups. No differences in the response categories over time in the other states were found during the follow-up in both study groups.

The likelihood-ratio tests indicated nonlinear patient-specific trajectories of HRQoL scores but not of the societal values of the EQ-5D-5L. There was no evidence for between-group differences over the course of the study in the mixed-effect models. Recipient age was significantly associated with a higher EQ-VAS score (**Table S1, SDC**, http://links.lww.com/TP/C753). Figure 3A and B visualizes the expected HRQoL scores and societal values of the EQ-5D-5L together with the corresponding observed values per time point and study group for the ITT population.

At 36 mo after transplantation, for both arms, the societal values of the EQ-5D-5L approximate those of the general Dutch population. This also applied to the patient's self-rated HRQoL scores as expressed with the EQ-VAS. The PP analysis showed comparable results (**Figure S1A and S1B, SDC**, http://links.lww.com/TP/C753). In the ITT population, LT recipients in the interventional arm approached the threshold for a clinically meaningful improvement (6.47 points) in the EQ-VAS score at 36 mo. LT recipients in the control group did not get near the threshold for a clinically meaningful improvement (4.98 points) in the EQ-VAS at 36 mo. In the PP population, LT recipients in the interventional arm reached the threshold for a clinically meaningful improvement (7.25 points) in

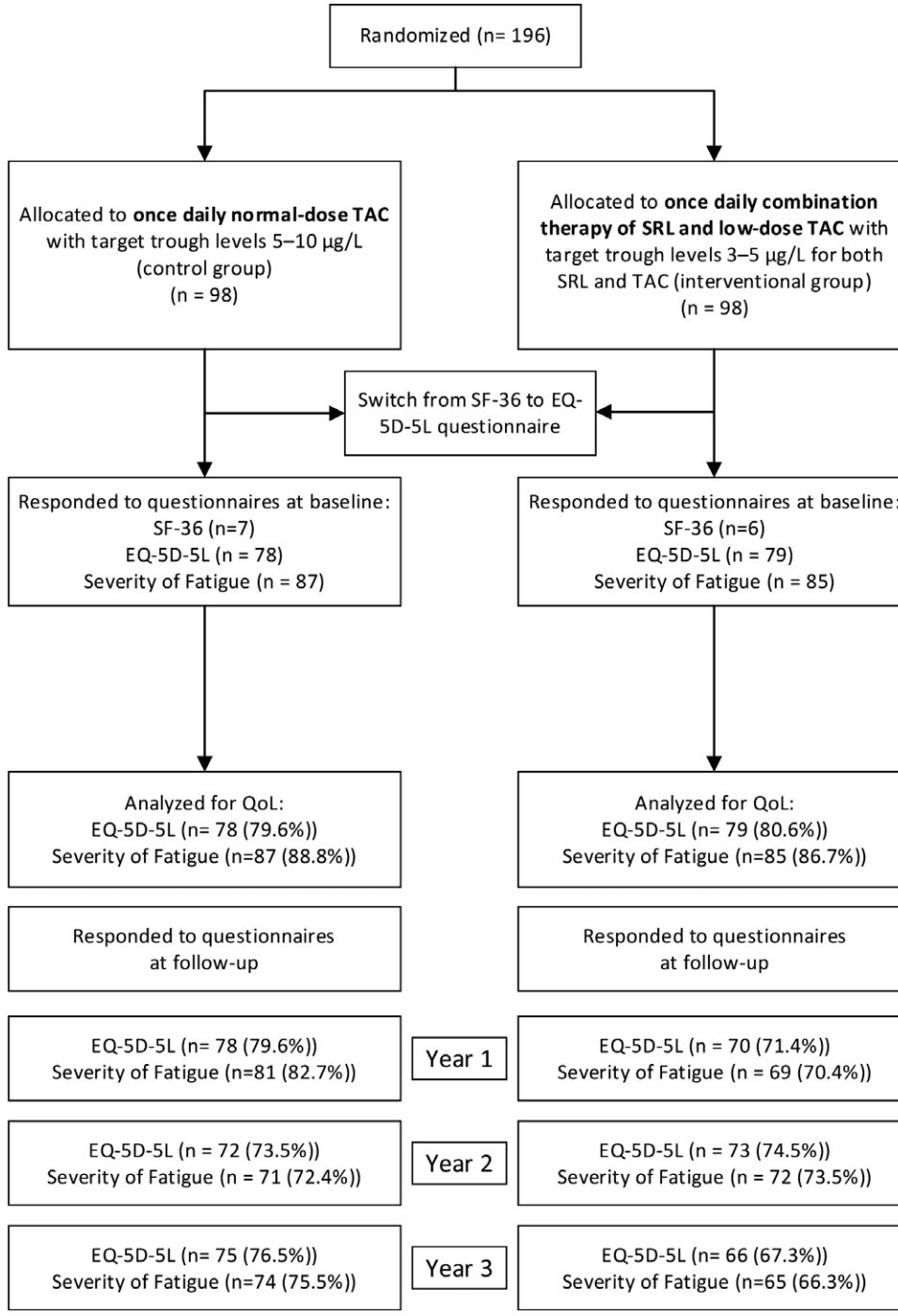

FIGURE 1. Enrollment, randomization, and follow-up. QoL, quality of life; SRL, sirolimus; TAC, tacrolimus.

the EQ-VAS score at 36 mo. LT recipients in the control group did not get near the threshold for a clinically meaningful improvement (4.30 points) in the EQ-VAS at 36 mo. A subgroup analysis was performed on LT recipients in the ITT population without diabetes. LT recipients without diabetes in the interventional group had a clinically meaningful improvement in the EQ-VAS score at 36 mo (8.1 points).

Severity of Fatigue

During the study, in the ITT and PP population, patients included in the interventional group did not report significantly lower fatigue scores than those in the control group (95% confidence interval [CI] for the ITT population −0.71 to 0.20 and 95% CI for the PP population −0.93 to 0.47). In the ITT population, the average score of the LT recipients in the control group reached clinical levels for fatigue, FSS ≥4.0 (Figure 4). These results persisted in the PP analysis (**Figure S2, SDC,** http://links.lww.com/TP/C753). In the ITT analysis, a minor decrease in the FSS over the course of the study is shown for both groups. Recipient age and hemoglobin concentration were significantly associated with a lower FSS in ITT analysis (**Table S1, SDC,** http://links.lww.com/TP/C753).

TABLE 1.

Baseline characteristics of the EQ-5D-5L and severity of fatigue at randomization

	EQ-5D-5L		Severity of fatigue	
	TAC (n = 78)	TAC + SRL (n = 79)	TAC (n = 87)	TAC + SRL (n = 85)
Recipient demographics				
Age, y (median, IQR)	56.5 (49.5–62)	55 (48–63)	56 (49–62)	54 (48–63)
Gender, male (n, %)	56 (71.8%)	53 (67.1%)	63 (72.4%)	60 (70.6%)
Primary disease (n, %)				
Hepatocellular carcinoma	27 (34.6%)	28 (35.4%)	30 (34.5%)	28 (32.9%)
(Non)alcoholic steatohepatitis	11 (14.1%)	12 (15.2%)	14 (16.1%)	14 (16.5%)
Primary sclerosing cholangitis	17 (21.8%)	15 (19%)	19 (21.8%)	15 (17.6%)
Acute liver failure	4 (5.1%)	9 (11.4%)	5 (5.7%)	10 (11.8%)
Cryptogenic cirrhosis	4 (5.1%)	3 (3.8%)	4 (4.6%)	4 (4.7%)
Metabolic disease	5 (6.4%)	4 (5.1%)	5 (5.7%)	4 (4.7%)
Viral hepatitis	2 (2.6%)	3 (3.8%)	2 (2.3%)	4 (4.7%)
Other[a]	8 (10.3%)	5 (6.3%)	8 (9.2%)	6 (7.1%)
NODAT, yes (n, %)	12 (15.4%)	5 (6.3%)	13 (14.9%)	5 (5.9%)
Preexisting diabetes, Yes (n, %)	11 (14.1%)	22 (27.8%)	12 (13.8%)	25 (29.4%)
Laboratory MELD (median, IQR)	16 (10–22)	16 (9.5–22)	16 (10–21.5)	18 (11–23)
Hemoglobin, mmol/L (mean ± SD)	7.6 ± 0.9	7.5 ± 0.8	7.6 ± 0.9	7.5 ± 0.8
eGFR, ml/min/1.73m2 (mean ± SD)	69 ± 16	72 ± 15	69 ± 16	71 ± 15
TAC, µg/L (mean ± SD)	7.7 ± 2.5	7.5 ± 2.9	7.7 ± 2.5	7.6 ± 2.9
Age, y (median, IQR)	54 (40–60)	52 (42–61.5)	54 (38.5–60)	53 (42–63)
Gender, male (n, %)	45 (57.7%)	43 (54.4%)	47 (54%)	44 (51.8%)
Type donation				
Donation after brain death (n, %)	46 (59%)	49 (62%)	54 (62.1%)	53 (62.4%)
Donation after circulatory death (n, %)	32 (41%)	29 (36.7%)	33 (37.9%)	31 (36.5%)
Living (n, %)	–	1 (1.3%)	–	1 (1.2%)
Cold ischemia time, min (mean ± SD)	415 ± 107	413 ± 129	419 ± 110	410 ± 134
Warm ischemia time, min (median, IQR)	29 (25–36)	27 (24–38)	29 (25–36)	27 (24–37.5)
Antihypertensive drugs, yes (n, %)	29 (37.2%)	23 (29.1%)	31 (35.6%)	23 (27.1%)
Corticosteroids, yes (n, %)	73 (93.6%)	74 (93.7%)	82 (94.3%)	80 (94.1%)
EQ-5D-5L score				
VAS (mean ± SD) [ref: 0–100]	74 ± 15	74 ± 15	–	–
Societal values of the EQ-5D-5L based on the Dutch tariff for the EQ-5D-5L (median, IQR) [ref: −0.466 to 1]	0.85 (0.75–1.00)	0.84 (0.75–1.00)	–	–
Severity of fatigue				
Question score (mean ± SD) [ref: 1–7]	–	–	4.0 ± 1.38	3.7 ± 1.44

eGFR, estimated glomerular filtration rate; IQR, interquartile range; MELD, model for end-stage liver disease; NODAT, new onset diabetes after transplantation; SRL, sirolimus; TAC, tacrolimus; VAS, visual analog scale.

[a]Other includes primary biliary cirrhosis, secondary biliary cirrhosis, autoimmune cirrhosis, and polycystic liver disease.

DISCUSSION

In this study, we found no evidence for differences between the HRQoL and the severity of fatigue for the combination of low-dose SRL and extended-release TAC compared with normal-dose extended-release TAC during 36 mo after transplantation. We could not confirm the beneficial effects of mTOR inhibitor–based regimens with an early conversion on HRQoL after LT, as suggested by Benzing et al.[9] The HRQoL of the transplanted patients approximates that of the general population at 36 mo after transplantation. Furthermore, LT recipients using the combination of low-dose SRL and extended-release TAC approached the threshold for a clinically meaningful improvement in the EQ-VAS score at 36 mo after transplantation.

In general, our HRQoL results are consistent with several reviews showing that the overall HRQoL does improve after LT to a similar level as the general population.[2,4,17] Li et al showed comparable results in kidney transplant recipients for the 5 states of the EQ-5D-5L questionnaire, with self-care and anxiety/depression as the states with the least problems and usual activities, pain/discomfort, and mobility the most problems.[18]

In contrast with the previously published results by van Ginneken et al, we show an improvement in the mean FSS at 3 y compared with baseline for both groups.[5] van Ginneken et al showed at baseline a mean FSS of 4.5 ± 1.6, whereas we find at baseline a mean FSS for the control group of 4.0 ± 1.4 and a mean FSS for the interventional group of 3.7 ± 1.4. At 2 y, van Ginneken et al showed no improvement in the mean FSS (4.5 ± 1.8) compared with the baseline levels. Because the study by van Ginneken et al was performed in 2010, these differences in findings likely originate from the improvements in patient care that have been made over the last 10 y. A possible explanation might be the lowering of the immunosuppressive dosages and the

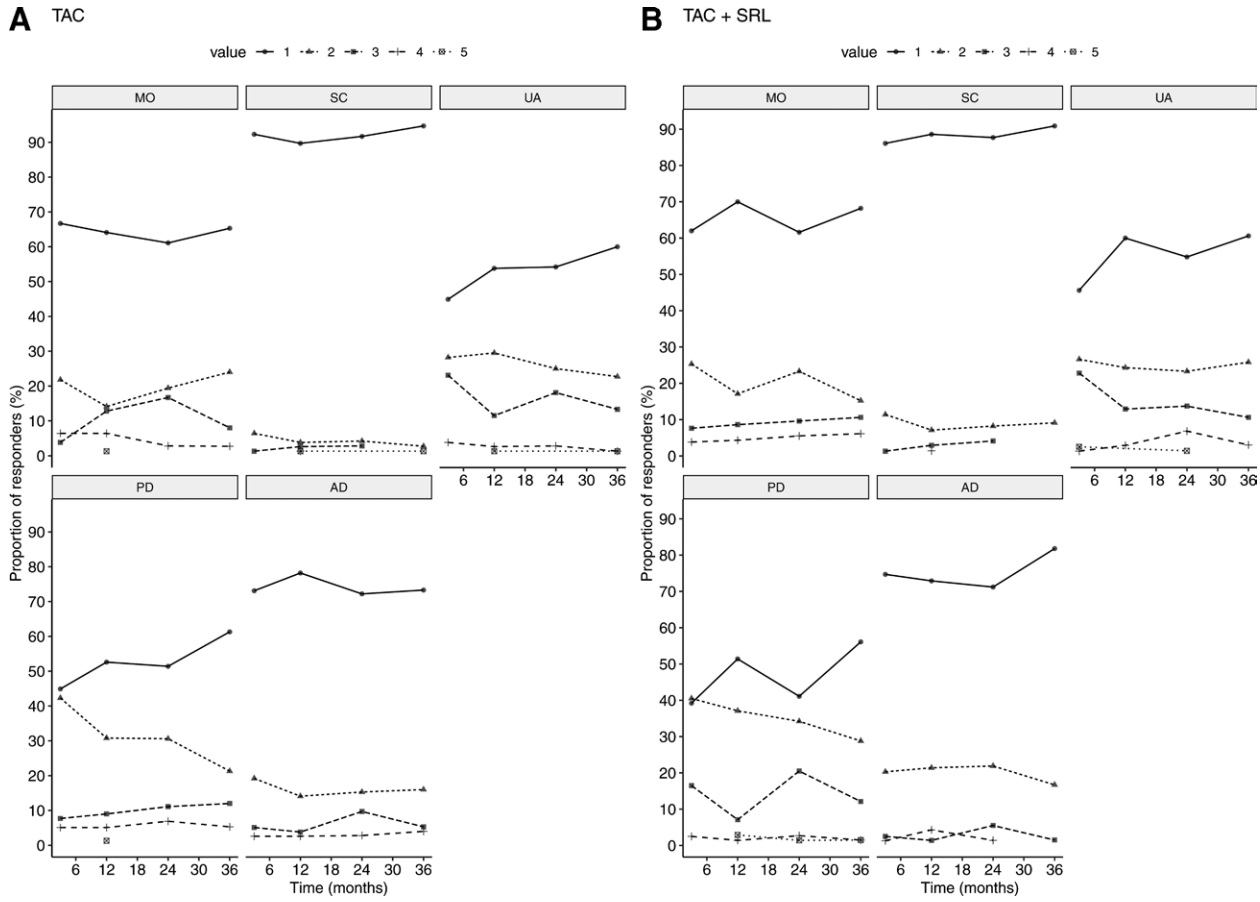

FIGURE 2. Proportion of responses by level of severity for EQ-5D-5L dimensions during the study period. A, TAC group (control group). 1, no problems; 2, slight problems; 3, moderate problems; 4, severe problems; 5, extreme problems. B, TAC + SRL group (interventional group). 1, no problems; 2, slight problems; 3, moderate problems; 4, severe problems; 5, extreme problems. AD, anxiety/depression; MO, mobility; PD, pain/discomfort; SC, self-care; SRL, sirolimus; TAC, tacrolimus; UA, usual activities.

introduction of a lifestyle outpatient monitoring program. However, long-term fatigue remains with a negative effect on the quality of life of LT recipients.

Until now, no universal MID has been described for the EQ-VAS.[13,19,20] Because no research has been done to describe the MID for the transplant population, we used a common threshold in the oncology research.[13] In the PP population, LT recipients in the interventional arm showed a clinically meaningful improvement in the EQ-VAS score at 36 mo. Interestingly, at 24 mo after transplantation, LT recipients in both study groups (interventional and control) reported a lower EQ-VAS score than the score at 12 mo in the PP and ITT analyses. A possible explanation might be that LT recipients in the second year after transplantation are confronted with the fact that not all health problems after LT will be resolved. LT recipients being 3 y after transplantation have accepted their new life and therefore report a higher score on their EQ-VAS score.

The HRQoL for LT recipients in both arms approximates that of the general Dutch population. This observation needs to be considered in the context of the indication for transplantation and the fact that many LT recipients develop comorbidities such as diabetes after transplantation. At the end of the study, 23.2% (46/198) of the LT recipients used diabetes medication compared with 32.3% (64/198) at baseline. Several studies showed that diabetes is associated with lower HRQoL scores in kidney transplant recipients and the general population.[18,21] As shown in our subgroup analysis for the ITT population, LT recipients without diabetes in the interventional group had a clinically meaningful improvement in the EQ-VAS score at 36 mo (8.1 points). The improvement in this subgroup was higher than the improvement in the ITT (6.47 points) or PP (7.25 points) population. The majority (54/67, 80.6%) of the LT recipients transplanted because of hepatocellular carcinoma (HCC) had received models for end-stage liver disease exception points. These HCC patients and primary sclerosing cholangitis patients are representing groups that generally report better HRQoL scores.[22,23] The reduction in patients using diabetes medication and the fact that the majority (>50%) of the patients included in this study were transplanted because of HCC or primary sclerosing cholangitis might have contributed to a high HRQoL and approximating that of the general Dutch population.

Tremor is the most important side effect of TAC affecting health dimensions of the EQ-5D-5L. This neurological side effect is dependent on the plasma concentration of TAC with higher TAC plasma concentrations resulting in more frequent and intense tremors.[24] Based on the fact that, in the interventional arm, the TAC plasma concentration is halved at randomization, one might expect that this could result in less problems in the health dimensions of mobility and usual activities in the interventional arm. However, we do not find differences between the study groups for these health

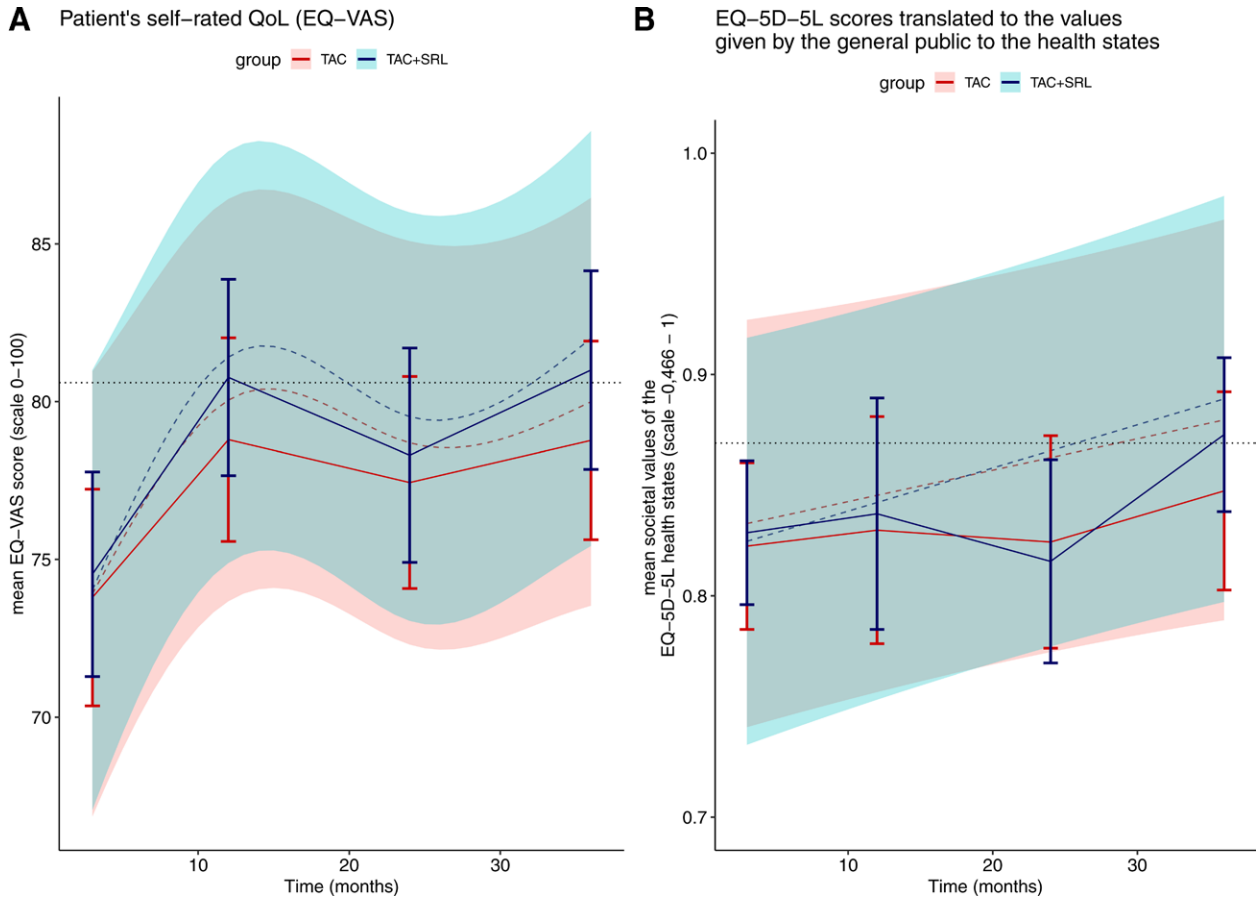

FIGURE 3. EQ-VAS score and EQ-5D-5L scores on the dimensions translated to the societal values for the intention-to-treat population. A, Patient's self-rated QoL (EQ-VAS). Group-wise mean EQ-VAS with 95% confidence interval (CI) during the course of the study represented as solid lines. The dashed lines and shaded areas indicate the expected values and corresponding 95% CI from the generalized mixed-effect model (values for the covariates: TAC trough levels, kidney function, hemoglobin, recipient age and sex, primary disease, the usage of antihypertensive and antidiabetic drugs, and the usage of corticosteroids, as well as the interaction between visit and the study group). Random participant effects were included to account for repeated measurements nested within each participant. The shape of the association with the EQ-VAS was investigated using natural cubic splines. Splines provide a convenient nonparametric way to flexibly model (potentially) nonlinear associations in regression models. Instead of using 1 polynomial (eg, a quadratic or cubic function) that spreads over the whole range of the covariate, splines use a set of several polynomial functions that are defined over smaller intervals. This allows the resulting fit to be more flexible than when using a single polynomial. Missing data were considered as missing completely at random. The dotted black line indicates the mean self-reported EQ-VAS score by the general Dutch population.[12] B, EQ-5D-5L scores translated to the values given by the general public to the health states. Group-wise mean of the societal values of the EQ-5D-5L health states with 95% CI during the course of the study represented as solid lines. The dashed lines and shaded areas indicate the expected values and corresponding 95% CI from the generalized mixed-effect model (values for the covariates: TAC trough levels, kidney function, hemoglobin, recipient age and sex, primary disease, the usage of antihypertensive and antidiabetic drugs, and the usage of corticosteroids, as well as the interaction between visit and the study group). Random participant effects were included to account for repeated measurements nested within each participant. The likelihood-ratio test indicated no need for a nonlinear association structure. Missing data were considered as missing completely at random. The dotted black line indicates the mean EQ-5D-5L score given by the general Dutch population to the health states.[12] QoL, quality of life; SRL, sirolimus; TAC, tacrolimus; VAS, visual analog scale.

dimensions. Overall, health dimensions in the EQ-5D-5L are influenced by many different factors, such as lifestyle, revalidation and physiotherapy, and personal characteristics (eg, coping strategies). Therefore, translating the EQ-5D-5L scores on the health dimensions to the societal values represents the HRQoL of the LT recipients the best.

This is the first randomized controlled trial in LT investigating patient-reported outcomes in the context of immunosuppressive drugs. Furthermore, the EQ-5D-5L scores on the dimensions were translated to the societal values, and we achieved a high response rate. Several limitations have to be addressed. First, in both study groups, almost half of the LT recipients had protocol violations in immunosuppressive therapy, which could have caused an underestimation or overestimation of the HRQoL and severity of fatigue. However, we believe this does not affect the interpretation of the results because the HRQoL for both groups is high, half of the patients in both groups switched immunosuppressive therapy, and the changes in immunosuppressive regimens reflect the daily clinical practice. Furthermore, we performed a PP analysis that showed comparable results to the ITT analysis. Next, we did not control for the use of medication, such as pain medication or the use of anxiolytic drugs, that might influence the response on the corresponding states in the EQ-5D-5L questionnaire. Unfortunately, it is not possible to determine to what extent these medications might have contributed to the results in both study groups.

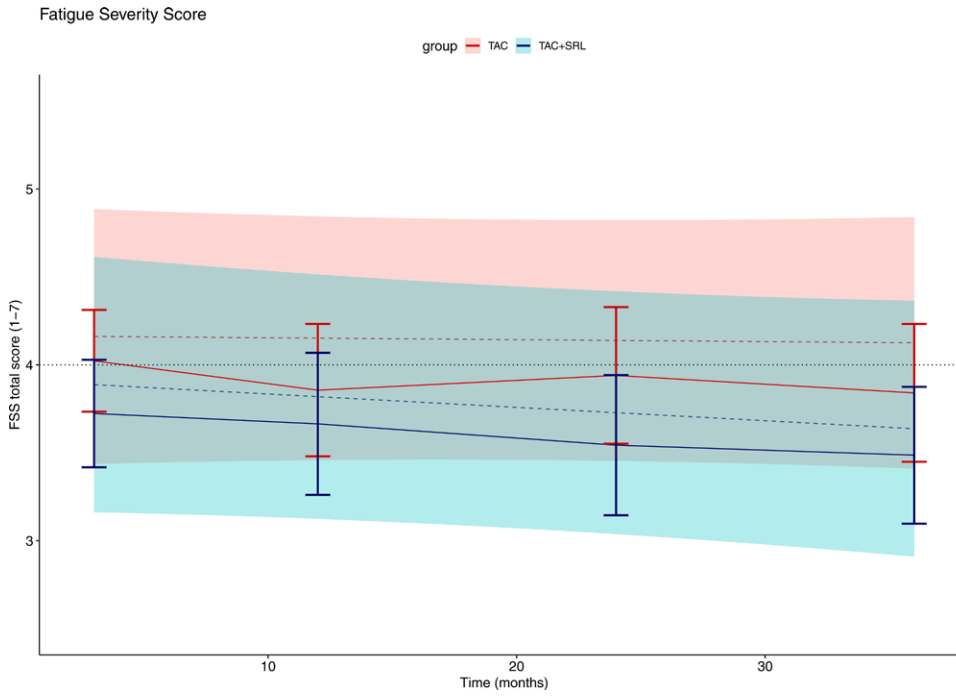

FIGURE 4. Severity of fatigue for the intention-to-treat population. Group-wise mean of the FSS with 95% confidence interval (CI) during the course of the study represented as solid lines. The dashed lines and shaded areas indicate the expected values and corresponding 95% CI from the generalized mixed-effect model (values for the covariates: TAC trough levels, kidney function, hemoglobin, recipient age and sex, primary disease, the usage of antihypertensive and antidiabetic drugs, the usage of corticosteroids, and the usage of MMF, as well as the interaction between visit and the study group). Random participant effects were included to account for repeated measurements nested within each participant. The likelihood-ratio test indicated no need for a nonlinear association structure. Missing data were considered as missing completely at random. The dotted black line indicates the clinical level for fatigue.[15] FSS, Fatigue Severity Score; SRL, sirolimus; TAC, tacrolimus.

In conclusion, in this study, the HRQoL and the severity of fatigue did not differ for an SRL-based regimen compared with a TAC-based regimen 36 mo after transplantation. The HRQoL of all transplanted patients in this trial approximated that of the general Dutch population, suggesting little to no residual symptoms in the long term after transplantation.

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