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## Assessment of health-related quality-of-life in patients after heart transplantation under therapy with tacrolimus or cyclosporine

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**Abstract** Reduction of allograft rejections remains a primary goal for patients after orthotopic heart transplantation. In an open, multi-centre, prospectively randomised, parallel group study, patients with primary orthotopic heart transplantation under oral immunosuppressive treatments with tacrolimus (FK506) or cyclosporine (sandimmun) were compared with respect to medical outcome data. As health-related quality-of-life (HRQOL) is also supposed to be an important outcome parameter, it was assessed as a secondary variable in these two patient groups. Patients' self-rated generic HRQOL was assessed 6 weeks, 3 months, 6 months and 12 months after surgery with the SF-36 questionnaire, a generic HRQOL instrument. For 70 patients (46 under tacrolimus, 24 under cyclosporine), intent-to-treat analyses were carried out. The tacrolimus group

showed improvements in the different HRQOL subscales of the SF-36 compared to the cyclosporine group. Especially the SF-36 subscales 'vitality' and 'mental health' showed statistically higher scores for the tacrolimus group. Aggregating psychological and cognitive subscales in the 'mental component score', patients treated with tacrolimus showed a statistically significant improvement compared to the cyclosporine group. The assessment of HRQOL variables in the evaluation of treatment effects proved to be an outcome parameter in this study. The results demonstrate the benefit of tacrolimus with respect to the HRQOL of patients, especially in the psychological dimension.

**Key words** Health-related quality-of-life · Heart transplantation · Tacrolimus (FK506) · Cyclosporine · Short-Form 36

### Introduction

Since the South African surgeon Christian N. Barnard carried out the first human heart transplantation in 1967, medical development has continually made good progress in this field. Today, heart transplantation is an accepted method of treating heart disease in its final stage [4, 5, 12]. These operations have been carried out in more than 16 000 cases [12]. Survival of heart recipients has continuously increased with both the development of immunosuppressive medicine, for example cyclosporine [2] or tacrolimus [13] which prevent rejection

of the transplanted organ, and early recognition of rejections by endocrine biopsy. Due to the improvement of medical and surgical treatment, survival rates range at about 85–90% in the 1st year, 80–85% in the 3rd year and 75–80% in the 5th year after transplantation. Since 1985 conventional therapy in heart transplantation has been based on cyclosporine A, which is, however, being associated with several disadvantages. This medication is usually supplemented by corticosteroids and azathioprine. The main adverse events related to the use of cyclosporine A are hypertension and nephrotoxicity, hyperlipidaemia and malignancy, of which the

latter two adverse events can also result from the combination of cyclosporine A and corticosteroid treatment. Developed in the late 1980 s, tacrolimus is regarded as a potential immunosuppressive drug that can be applied over longer periods of time. In kidney transplants, tacrolimus has already been successfully introduced as an immunosuppressant [14, 23]. Until now patients with heart transplants have rarely been treated with tacrolimus. However, in some studies conventional therapy has successfully been substituted by tacrolimus.

As immunosuppressive drugs have to be administered over longer periods of time, side effects and toxicity associated with immunosuppressive drug therapies and the occurrence of rejection episodes have a large impact on patients' lives and their perception of health and well-being. Therefore effects of immunosuppressants on different aspects of health-related quality-of-life (HRQOL) after cardiac transplantation have to be investigated. HRQOL has been defined as a self-reported evaluation of at least four domains of human life: physical state, psychological well-being, social relations and functional capacity in everyday life [3, 7]. v. Steinbüchel [15, 16] added the mental component to this definition which is especially relevant to patients with cardiovascular diseases. Although there is still no golden standard for these dimensions, there is consensus that HRQOL can be investigated with generic and disease-specific instruments. Generic health measures assess basic health values, physical and psychological functioning, ability to fulfil one's role as a spouse, parent or worker, and social functioning. These instruments usually show a high degree of sensitivity to conditions having an impact on functional status and well-being [18]. Generic measures are useful to compare outcomes with regard to a wide range of health states. On the other hand, disease-specific instruments are sensitive to specific aspects of disease and/or a particular treatment. Several studies have described the impact of heart transplantation on patients' generic and specific HRQOL [5, 8, 9].

The importance of the psychological component in the treatment of heart transplant patients for example is stressed in a study reported by Leedham et al. [11]. Patients' positive expectations before transplantation had a positive effect on the adjustment to the illness, on compliance with a complex medical regimen, on the patients' mood and on the HRQOL, even in those patients who did suffer from health setbacks.

Walter et al. [17] summarise the outcome of the international symposium on "health-related quality of life after open heart surgery". They state that independent of the type of transplant, patients do generally benefit from early identification of psychological impairment, psychological counselling before and after the surgery and from socio-economic strategies to facilitate re-entry to work. However, not only major surrounding circumstances, but also even subtle cognitive or neuropsychological

deficits may have a major impact on adherence to medical regimens, psychosocial adjustment, and HRQOL of patients, as demonstrated in a study by Farmer [6]. Grady et al. [9] found in a study on predictors of HRQOL in patients after heart transplantation that primarily psychological variables explain the HRQOL at year 1 after heart transplantation. Additional variance in HRQOL was explained by physical, somatic sensation, demographic and health status variables.

The impact of different immunosuppressants (tacrolimus vs cyclosporine) on the HRQOL has been investigated for patients after liver transplantation [8, 13] and kidney transplantation [14]. Until now however, HRQOL of patients treated with cyclosporine A compared to tacrolimus after heart transplantation has not yet been reported on, neither the generic nor the disease-specific aspects. Therefore, the aim of the study was to compare the impact of cyclosporine-based or tacrolimus-based therapy on HRQOL of patients after heart transplantation. The second objective was the evaluation of changes over time in HRQOL associated with heart transplantation and immunosuppressive therapy. Due to logistic constraints of this clinical trial, especially temporal ones, it was decided to concentrate on measuring the generic aspects of HRQOL only.

## Material and methods

### Study design

It was a phase II, open, multicentre, randomised, controlled, parallel group study of a 1-year treatment in patients who have undergone heart transplantation. Patients were randomised to either tacrolimus or the reference medication cyclosporine A.

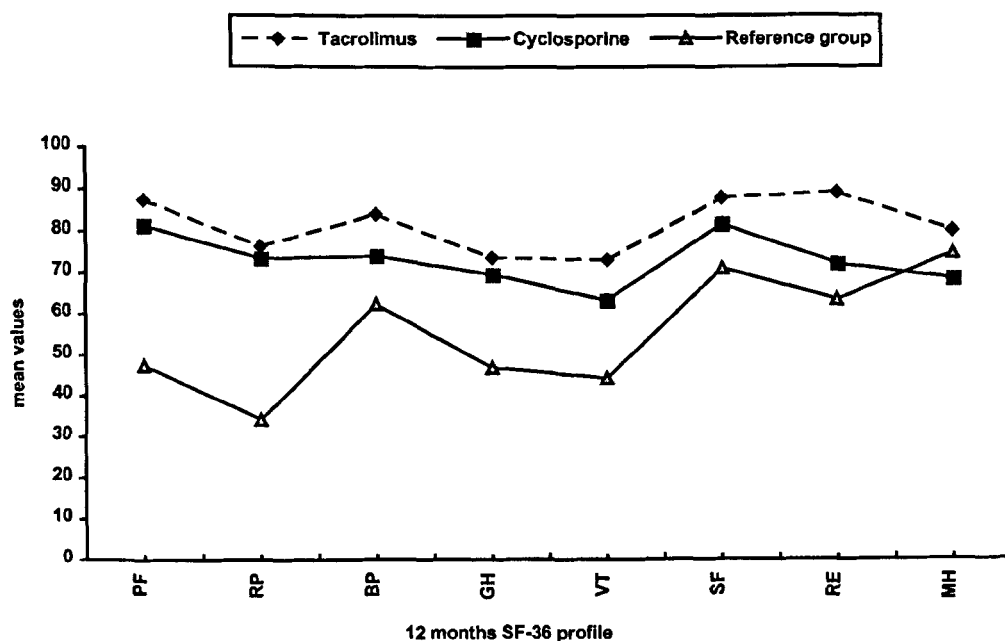
### Patients

Patients with a primary diagnosis of end-stage heart disease were eligible for primary heart transplantation. Included were male and female patients aged 18 years or older. Patients who participated in the clinical trial were asked to take part in the HRQOL investigation. The patients were informed in detail about the HRQOL assessment. Seventy patients were enrolled in the study and randomised in a ratio of 2:1 on the tacrolimus group ( $n = 46$ ) or on the cyclosporine A group ( $n = 24$ ). Five centres participated in the recruitment of the patients. Patients who did not respond to the immunosuppressive therapy were withdrawn from the study.

### HRQOL instrument

For the generic HRQOL assessment, the SF-36 questionnaire, a well-tested international instrument with good psychometric quality was chosen [18]. As it has been validated for a variety of languages, its use guarantees comparability with other HRQOL studies. The SF-36 consists of eight subscales which measure health concepts in the following dimensions: physical functioning (10

**Fig. 1** SF-36 profile of eight subscales after 12 months. *PF* physical functioning, *RP* role physical, *BP* bodily pain, *GH* general health, *VT* vitality, *SF* social functioning, *RE* role emotional, *MH* mental health, *reference group* congestive heart failure patients [19]



items), role-physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role emotional (3 items) and mental health (5 items). The eight subscales can furthermore be aggregated to two component scores, the physical component score and the mental component score. Responses to questions within scales were aggregated and linearly transformed to scale scores ranging from 0 (representing poor health status) to 100 (representing optimal health status). The analysis of the SF-36 was scored using the published algorithms [19, 20].

#### HRQOL questionnaire administration

The questionnaire was administered at four visits: 6 weeks after transplantation, followed by assessments at 3, 6 and 12 months after surgery. Each patient was instructed by competent personnel (for example doctor, nurse or study co-ordinator). All items of the questionnaire were rated by the patients themselves. The study person in charge filled in the patient's study number and initials, and indicated the visit/time point for which each assessment was applicable. Any further interventions were avoided.

#### Statistical analysis

For SF-36 subscores and summary scores, descriptive as well as confirmatory analyses were performed. With respect to confirmatory statistics, analyses of variance (ANOVA) over time were performed as well as *t*-tests. The *t*-tests were administered for within-treatment-group comparisons, underlining the change over time for each treatment group separately. A nominal descriptive significance level of 0.05 was used to identify interesting differences. Analyses of variance with repeated measurements was applied according to Winer [21]. In order to compare the treatment groups over the SF-36 scales and the two component scores, least square means were calculated and assessed. The analysis of covariance used as covariate the baseline value at 6 weeks. The results for the analysis involving "last value" using the last obtainable value of

the patient [last value carried forward (LVCF)] provide a conservative estimate of the outcome of the study after 12 months including all patients, regardless of whether or not they survived the whole study period.

## Results

### Description of the SF-36 profile for the different assessment points

For the eight SF-36 subscale scores, treatment group differences at the last assessment point are compared descriptively (see Fig. 1). At the 6-week visit, data showed an almost identical profile for the two treatment groups with a slight advantage for the tacrolimus group in the subscales "role physical", "bodily pain" and "general health perception". In "physical functioning", "vitality" and "role emotional", the cyclosporine group appeared to be superior to the tacrolimus group (Table 1). At the end of the trial the mean scale values for the tacrolimus group were all higher on a descriptive level than those of the cyclosporine group. This difference in the two treatment groups was already apparent at the 3-month assessment point and remained constant.

At the 12-month assessment, patients treated with tacrolimus showed higher mean subscale scores than the cyclosporine group, suggesting that their HRQOL was in all HRQOL dimensions better than in the patient group treated with cyclosporine. Compared to the reference group of congestive heart failure [19], HRQOL in both treatment groups was higher. Note however that no statistical significance was applied here.

**Table 1** *T*-tests within groups. Assessment point 1 vs assessment point 4 or last value

Health concept	6 weeks vs 12 months		6 weeks vs last value	
	Tacrolimus	Cyclosporine	Tacrolimus	Cyclosporine
Bodily pain	62.2 vs 84.2**	49.0 vs 74.7*	62.2 vs 77.3*	49.0 vs 69.1*
Health perception	69.9 vs 73.9	64.8 vs 69.7	69.9 vs 70.8	64.8 vs 62.8
Mental health	77.7 vs 80.1	75.0 vs 68.4	77.7 vs 77.3	75.0 vs 65.0
Physical functioning	<b>61.1 vs 87.6***</b>	67.4 vs 81.4	<b>61.1 vs 82.0**</b>	67.4 vs 75.5
Role emotional	<b>61.6 vs 89.2**</b>	66.7 vs 72.2	<b>61.6 vs 82.2*</b>	66.7 vs 66.7
Role physical	43.9 vs 76.5**	32.5 vs 73.6**	43.9 vs 70.6*	32.5 vs 69.8**
Social functioning	<b>73.7 vs 88.2*</b>	75.6 vs 81.9	73.7 vs 82.1	75.6 vs 75.0
Vitality	<b>59.1 vs 73.5**</b>	64.3 vs 63.6	<b>59.1 vs 69.7*</b>	64.3 vs 56.9
Mental component	50.6 vs 53.9	51.8 vs 47.8	50.6 vs 52.1	51.8 vs 45.6
Physical component	40.2 vs 50.5***	38.8 vs 49.6**	40.2 vs 48.4**	38.8 vs 47.1*

\*  $P \leq 0.05$ \*\*  $P \leq 0.01$ \*\*\*  $P \leq 0.001$ **Table 2** Between-treatment comparison. Analysis of variance and analysis of covariance for all time points: least square means

Health concept	ANOVA (all time points)		ANCOVA Baseline vs 12 months (Baseline vs last value)	
	Tacrolimus	Cyclosporine	Tacrolimus	Cyclosporine
Bodily pain	70.4	62.4	82.1 (75.4)	74.5 (72.1)
Health perception	70.3	63.3	71.9 (69.8)	71.00 (66.5)
Mental health	<b>77.1*</b>	<b>67.8</b>	<b>79.7** (77.0)*</b>	<b>67.5 (67.4)</b>
Physical functioning	74.3	70.4	87.8 (82.0)	80.1 (76.1)
Role emotional	74.2	64.7	89.6 (82.5)	73.3 (72.4)
Role physical	57.0	49.9	74.6 (69.0)	74.1 (72.3)
Social functioning	78.0	70.8	86.7 (81.0)	81.4 (77.6)
Vitality	65.6	57.0	<b>74.4** (71.1)*</b>	<b>63.0 (59.4)</b>
Mental component	51.5	47.3	<b>53.9** (52.3)*</b>	<b>46.8 (46.3)</b>
Physical component	44.7	43.0	49.9 (47.8)	51.4 (49.2)

\*  $P \leq 0.05$ \*\*  $P \leq 0.01$ \*\*\*  $P \leq 0.001$ 

#### Within-group tests (assessment 6 weeks vs assessment 12 months or last value; Table 1)

Within-group tests were calculated for all eight subscales of the SF-36 and the mental and the physical component score. The relative improvements in "pain index" and "role physical" over time were statistically significant for both groups (within-group *t*-test). Additionally, a significant increase in level only for the tacrolimus-treatment group in "physical functioning", "role emotional", "social functioning" and "vitality" could be observed. A within-group *t*-test using the LVCF instead of the 12-month value showed almost identical results (the only exception being tacrolimus "social functioning"). This is also a confirmation of the fact that any possible difference in drop-out mechanism between the two groups did not influence the results of these analyses.

#### Between-treatment comparisons (ANOVA and ANCOVA)

Table 2 displays the least square means from the repeated measure analysis of variance over all time points. The least square means represent overall treatment levels. The subscale for "mental health" showed a statistically significant difference between the treatment groups. Table 2 also demonstrate the results of an ANCOVA, which included the baseline value as a covariate; the dependent variable was either the 12-month value or the LVCF. These analyses show statistically significant differences between the treatment groups in "mental health", "vitality" and the "mental component score".

#### Discussion

HRQOL of patients after heart transplantation has been studied over the past 15 years [9]. The present study provides encouraging results with respect to the

comparison of treatments showing beneficial effects of both treatments. Patients treated with tacrolimus showed more pronounced and faster improvement in all HRQOL dimensions measured with the SF-36 than patients treated with cyclosporine. Compared to the reference group of patients with congestive heart failure at the last assessment point, a better health status is observed for both treatment groups.

Both drugs affected the "role physical" and the "bodily pain" subscales in the patients in a positive way. Being free of pain or feeling less pain and being able to participate in daily life activities and work can be regarded as core elements of a patient's well-being. The improvement over time for "physical functioning", "role emotional", "social functioning" and "vitality" in the tacrolimus group and not in the cyclosporine group can be seen as specific advantage of the tacrolimus treatment. The comparison between therapies also reveals a statistically significant subjective health evaluation for patients treated with tacrolimus in terms of "mental health". This means that these patients generally feel happier and calmer. This positive influence of tacrolimus on emotional and mental activities is also underlined by a statistically significant group difference for the mental component score which was not present in the physical component score. These results are very similar to those obtained from the Pittsburgh centre study [1, 22], where an investigation was initiated to examine the general HRQOL of patients with heart transplants under tacrolimus therapy. The HRQOL of 26 patients who received tacrolimus following heart transplantation was compared to 22 patients who received conventional therapy with cyclosporine A, azathioprine and prednisone. HRQOL was assessed by an ad hoc constructed questionnaire at 2 and 7 months posttransplantation, covering the areas of physical, psychological and social well-being. HRQOL was comparable in both treatment arms at 2 months posttransplant whereas, after 7 months, significant differences were detected: patients with tacrolimus treatment reported a higher degree of mobility and overall physical functioning. They showed less anxiety, less depression, less anger and less hostility. The degree of social withdrawal and unhappiness about their physical appearance was significantly

lower in tacrolimus patients. Most importantly, more patients in the tacrolimus group were able to resume work. The actual study and the Pittsburgh trial stress the benefit of tacrolimus as compared to alternative medications. These studies especially agree on the additional benefit of improvement of social and emotional components of HRQOL.

Larsson and colleagues [10] identified the nine concerns of transplant patients as follows: "end-stage heart disease", "family worrying", "illness symptoms", "waiting for a donor", "uncertainty about the future", "no energy for leisure activities", "constantly feeling worn out", "less control over life" and "dependency on others". It would seem that those SF-36 subscales that showed statistically significant differences are probably closely related to the afore-mentioned patients' relevant problems. The positive influence of similar psychological variables (for example care and support by one partner, self-control, emotional stability, etc.) on later medical outcomes was documented by the same research group [10].

In the present study the magnitude of the significant differences between treatment groups was 12 points on the 0–100 SF-36 scale range. This reflects not only a statistical difference but also a difference of clinical relevance [18]. In the general perspective of HRQOL scores, the group treated with tacrolimus showed both a faster and larger improvement in well-being as compared to the group treated with cyclosporine. Although the cyclosporine group showed in some subscales higher scores at the first assessment point, the tacrolimus-based therapy was associated with a superior effect on HRQOL during the whole course of the study. It seems that the positive effect of tacrolimus relative to cyclosporine is most prominent after 12 months of therapy. These results, showing the greater efficacy of tacrolimus in comparison to patients treated with cyclosporine after heart transplantation, not only encourage the inclusion of HRQOL-outcome variables in treatment evaluations, but also suggest a beneficial effect of tacrolimus in patients after heart transplantation.

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