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LCP-tacrolimus in long-term kidney graft recipients: Dosing and adherence

Yvonne Schill [a,†], Mario Schiffer [b,†], Lars Pape [c,†,*]

[a] Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, 30625 Hannover, Germany
[b] Department of Nephrology, University Hospital of Erlangen, Erlangen, Germany
[c] Clinic of Pediatrics II, Essen University Hospital, Essen, Germany

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ABSTRACT

Introduction: The new LCP-formulation of tacrolimus (Tac) has shown pharmacokinetic advantages in patients after liver transplantation that are associated with better adherence. The influence of prolonged release Tac on adherence, trough levels and dosing of Tac remains unclear.
Methods: A prospective study was performed in 62 patients from two centers, who were switched to LCP-Tac after kidney transplantation, to assess adherence as defined by the Tac trough level coefficient of variation (CoV) (primary endpoint) and BAASIS© Score, as well as kidney function, Tac trough level and tacrolimus dose.
Results: BAASIS© Score and Tac trough level CoV demonstrated good adherence over the study period, with no difference between the study timepoints (0.26 ± 0.16 at study start and 0.26 ± 0.11 at study end, $p = 0.976$, paired *t*-test). Graft function and Tac trough levels remained stable, and Tac dose could be reduced.
Conclusions: A switch to LCP-Tac is feasible and leads to stable adherence, graft function and Tac trough levels, in combination with lower Tac doses.

1. Introduction

Kidney transplant recipients in particular require lifelong immunosuppression, in which calcineurin inhibitors such as tacrolimus (Tac) play an important role. Tac is usually administered twice daily using an intermediate release (IR) formulation. The newer prolonged release (PR) formulation is also a reliable option but associated with a high dose and trough level inter- and intraindividual variability as well as with higher dosing requirements compared to IR-Tac [1]. LCP-Tac (Envarsus®), a new once-daily formulation of Tac, has recently become available. Using the so-called MeltDose technology, it has been approved as immunosuppressive medication for patients after kidney and liver transplantation [2]. LCP-Tac provides the same therapeutic effectiveness as the conventional twice-daily IR-Tac formulation (Prograf®), but with improved bioavailability, a more consistent pharmacokinetic profile, and reduced peak to trough, potentially leading to reduced Tac dosing and subsequently less calcineurin inhibitor-related toxicity [3]. A randomized controlled trial has proven that LCP-Tac can achieve similar outcomes in newly kidney transplanted patients with lower dose requirements [4].

Since other once- rather than twice-daily drug formulations lead to a significant improvement in adherence, LCP-Tac might also show similar improvements. Variation coefficients of immunosuppressive agent levels have been proven to be one of the best objective measures of adherence [5] as physicians often fail to estimate the level of adherence adequately [6]. Therefore, it can be speculated that, after kidney transplantation, LCP-Tac would lead to a lower Tac trough level Coefficient of Variation (CoV), representing more reliable immunosuppression. This could lead to more stable graft function, and fewer patients developing de novo donor-specific HLA- and non-HLA antibodies in the long run.

The ultimate goal of better adherence would be longer graft survival after kidney transplantation. This study focuses on the analysis of LCP-Tac treatment in long-term kidney transplant patients who were switched from IR-Tac.

2. Patients and methods

This study was an analysis of data generated during a prospective, observational, non-interventional trial. Tac levels, creatinine levels and eGFR values were collected and estimated every 3 months for twelve months. Post-kidney transplantation patients who had been switched by

* Corresponding author at: Clinic of Pediatrics II, Essen University Hospital, Hufelandstrasse 55, 45147 Essen, Germany.
E-mail address: Lars.Pape@uk-essen.de (L. Pape).
† These authors contributed equally to this work and share first authorship.

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a clinician to LCP-Tac were asked to participate in this study.

Patients were included in the study based on the following criteria: adult kidney transplant recipients switched to LCP-Tac in the last three months before study start willing to participate in the study by signing an informed consent. All other medications approved for using in combination with Tac were allowed. The exclusion criteria were as follows: children, pregnant women and patients with a known non-adherence as defined by the treating physician.

At the beginning of the study, we collected the following participant data: age, sex, time since transplantation, adherence to LCP-Tac via Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS®) Score, LCP-Tac dosage, Tac trough levels, creatinine levels, eGFR levels. Data, such as Tac trough levels, creatinine levels, eGFR levels and LCP-Tac dosage were collected every 3 months for one year. At the 3 months visits, all routine Tac levels acquired between the actual and the last visit were documented.

2.1. Primary efficacy variable

The individual CoV for immunosuppressive agent levels. The Tac trough level CoV (primary endpoint) was calculated at beginning and end of study period, based on at least the first three and the last three measurements.

2.2. Secondary efficacy variables

Initially we determined participant adherence by an analysis of the BAASIS® Score [7]. BAASIS® is a self-reporting instrument for measuring non-adherence to immunosuppressive drugs in transplant recipients. The BAASIS® self-reporting questionnaire is composed of four dimensions of immunosuppressive drug use (taking adherence, drug holidays, timing adherence and dose reduction) within a fixed period over the last four weeks. The outcome variable is non-adherence. The questionnaire was selected because it is short, with a good level of reliability, validity and sensitivity to timing and taking, the last of which are especially important for immunosuppressive regimes after kidney transplantation.

The estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) formula, with body surface area normalization (mL/min/1.73 m^2).

2.3. Sample size calculation

We first estimated the likely therapy adherence rate based on a group of patients on immunosuppressive therapy. Data from Hannover Medical School showed that half of the selected patients showed very good adherence, with a mean CoV (%) of 0.13 (±0.03), whereas poor compliance was observed in the other half of patients, with an average CoV (%) of 0.5 (±0.03). In a cross-sectional analysis based on self-assessments using the BAASIS© Score in patients from Hannover Medical school we identified 36% of patients with impaired adherence [4]. These values were taken as roughly predictive of the variance we would observe in our study. Assuming a population consisting of 50% with very good compliance, 25% with average compliance, and 25% with poor compliance, we simulated a mixed distribution with the statistical values above and calculated an average CoV (%) of 0.26 with a standard deviation of 0.15. Our expectation was that the use of LCP-Tac would increase the percentage of patients with good adherence. For that reason, we assumed the following positively shifted distribution (in%) for the PLCP-Tac group: 70:30:0 of very good/average/poor compliance. This distribution corresponds to a CoV (%) of 0.181 with the same standard deviation of 0.15. Assuming a two-sided type I error of 5%, a Student's two-sample *t*-test would have 80% power. Hence, recruitment of a total of 114 kidney transplanted patients was planned for this trial.

This study involves human participants. The study design was reviewed and approved by the Ethics Committee of Hannover Medical School (primary ethics vote, number 3493–2017) and the University Hospital Erlangen. The participants provided their written informed consent to be included in this study.

3. Results

3.1. Participants

At the beginning of the study, 62 transplant patients from two centers (Hannover Medical School and University of Erlangen), who were receiving LCP-Tac, gave their consent to participate. Eleven patients were excluded due to withdrawing their consent ($n = 2$), death due to a cardiovascular event ($n = 1$) or insufficient number of Tac trough levels to calculate CoV ($n = 9$) or a switch of transplant center ($n = 2$).

Our sample was therefore composed of 51 kidney transplant participants. The participant characteristics are reported in Table 1. Our sample consisted of 25 women (49%) and 26 men (51%) with a mean age of 48.1 years, a mean time since transplantation of 25.7 months and a mean daily dose of LCP-Tac of 5.1 mg. The patients had a mean Tac trough level of 7.5 µg/l, a mean creatinine level of 149.8 µmol/l and a mean eGFR of 47.4 ml/min/1.73m^2, while 22.9% of these participants exhibited an eGFR below 30 ml/min/1.73m^2.

3.2. Primary endpoint

The mean Tac trough level CoV was 0.26 ± 0.16. at study start and 0.26 ± 0.11 at study end ($p = 0.976$, paired *t*-test) based on 3–10 measurements per patient (Fig. 1). Data on Tac levels under IR-Tac before study start were not part of the study design.

3.3. Secondary endpoints

At the beginning of the study, we aimed to validate the BAASIS® to estimate immunosuppressant (non-)adherence in the participants. The results are shown in Table 2. The BAASIS® questionnaire revealed that 14% of participants were classified as non-adherent, 6% of the participants had missed a dose in the last month, 2% had skipped two or more doses in a row, 8% had taken their dose more than 2 h before or after the prescribed time and 2% had altered their dose. In the patients, classified as non-adherent, CoV at study start was numerically higher than in the whole group (0.32 ± 0.18 vs. 0.24 ± 0.15, p = n.s.)

To validate whether IR-Tac treatment had an effect on the dosage one year later, we compared the LCP-Tac dosage at beginning and end of

Table 1
Patient characteristics.

Variable	All ($n = 51$)
Age	
Mean (SD)	48.1 (14.6)
Median (IQR)	52.0 (23)
Sex Female,%	49 ($n = 25$)
Time since transplantation, months	
Mean (SD)	25.7 (31.1)
Median (IQR)	17.0 (22)
Tacrolimus dose, mg/d	
Mean (SD)	5.1 (4.5)
Tac trough levels, µg/l	
Mean (SD)	7.5 (2.5)
Creatinine, µmol/l	
Mean (SD)	149.8 (57.4)
eGFR (CKD-EPI), ml/min/1.73m^2	
Mean (SD)	47.4 (20.9)
Median (IQR)	46.0 (25.4)
eGFR <30 ml/min/1.73m^2,%	22.9

SD, standard deviation; IQR, interquartile range; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

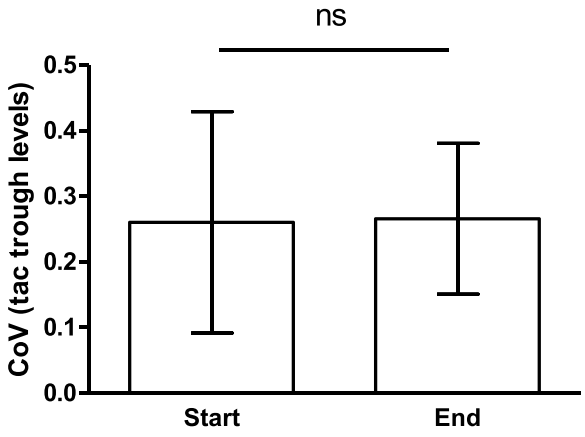

Fig. 1. Coefficient of Variation (CoV) of tacrolimus (tac) trough levels at beginning and end of the study. The bar graphs represent mean +/- SD (paired *t*-test).

Table 2
Non-adherence at study start measured by the BAASIS© Score.

Part 1		Response n (%)	Categorized as non-adherent n (%)
1	Taking dimension: Do you remember missing a dose of your immunosuppressive medication (IM) in the past 4 weeks? (i) Once per month	3 (6.1)	3 (6.1)
2	Drug holidays: Do you remember having skipped two or more doses of your IM in a row in the past 4 weeks? (i) Once per month	1 (2.0)	1 (2.0)
3	Timing dimension: Do you remember having taken your IM more than 2 h before or after the prescribed dosing time in the past 4 weeks? (i) Once per month (ii) Every second week (iii) Once per week (iv) More than once per week	2 (4.1) 1 (2.0) 1 (2.0)	4 (8.2)
4	Reduction of the dose: Have you altered the prescribed amount of your IM during the past 4 weeks without your doctor telling you to do so? (i) Once per month (ii) Every second week	1 (2.0)	1 (2.0)
	Total		**7 (14.3)**

the study. We could only analyze data from 32 patients due to incomplete data.

The mean LCP-Tac dosage was 4.98 ± 4.57 at study start and 3.34 ± 2.39 at study end showing a reduction in Tac dosage during the study ($p = 0.0134$, paired *t*-test). Tac trough levels remained stable during observation time with 7.5 ± 2.6, 6.5 ± 1.8, 6.4 ± 2.9, 5.7 ± 1.7 and 6.9 ± 2.0 ng/ml, 0, 3, 6, 9 and 12 months, respectively, after study start.

We could detect a numeric but non-significant increase in mean s-creatinine during observation time from 150 to 177 mmol/l ($p = 0.147$, paired *t*-test). eGFR was stable during observation time with a slight numeric decrease from 47 ± 21 to 43 ± 23 ml/min/1.73m^2 from study start to study end ($p = 0.412$, paired *t*-test).

During the study period, no acute rejections and two hospitalizations because of infections have been recorded in the participants and 8/11 excluded patients where data sets were available over the complete study period. No patient has developed de novo DSA.

4. Discussion

We could show stable Tac trough levels after switch to LCP-Tac. GFR was stable with a non-significant decrease of 4 ml/min over one year's observation time. This is comparable to – or even better than – normal GFR loss in kidney transplant recipients [8]. Our data therefore proves that LCP-Tac could be implemented safely after kidney transplantation in a cohort of patients initially treated with IR-Tac as has been demonstrated in patients switched directly after transplantation [4].

The primary endpoint of this study was to prove the hypothesis that treatment with LCP-Tac leads to an increase in adherence as expressed by the Tac trough level CoV over one year of treatment. However, we could not show any improvement in the CoV, which might have been due to the small numbers of participating patients in combination with a cohort with already good adherence willing to take part in this study. Interestingly, the CoV of Tac trough levels in our patients at study start and end exactly matched those published previously [6] under a standard immunosuppressive regimen. This was combined with a significant decrease in LCP-Tac dose during observation time showing that, in adherent patients, lower doses of LCP-Tac seem to be required to achieve the same Tac exposure even one year later. This is especially interesting, as both centers implemented a standard of using a conversion factor of 0.7 when switching from IR-Tac to LCP-Tac. For this finding we have actually no convincing explanation. The BAASIS© Score shows very good adherence at study start, with only 14.2% of patients with adherence problems, which is better than published data [7] and different to the result of the surrogate marker CoV that we used as a primary endpoint. Obviously, we cannot rule out a selection bias of primarily adherent patients agreeing to take part in the study. This could explain the good adherence rates even at study start using the BAASIS© Score. However, our study proved that satisfactory medication adherence could be secured under LCP-Tac treatment, leading to a lower dosage after one year and reducing the need for any nephrotoxic agent.

Interestingly, our study population was quite young, with satisfactory graft function and a short period between transplantation and study start, making the participants more predisposed to take part. Consequently, the results of this study may not be easily transferred to all patient populations.

5. Limitations

This study was a non-randomized trial that included only selected patients that were switched for clinical reasons to LCP-Tac. This design leads to a possible bias that has to be taken into account. In addition, there was a selection bias towards adherent patients during the recruitment period as an initial evaluation in a random patient sample from Hannover Medical School demonstrated worse adherence. Unfortunately, it was not possible to include all the 114 patients as initially planned and calculated as the sample size, as only a smaller number of patients were treated with LCP-Tac in both study centers which led to an underpowered study. This might have led to the lack of statistical differences in our primary endpoint. Due to organizational difficulties, we did not manage to evaluate the BAASIS® Score at the end of the study in a sufficient number of patients for the analysis. The study design did not include a retrospective analysis of data under IR-Tac treatment or a randomized control group with IR-Tac treatment, so that it is not possible to make a comparison of results for the same period.

No complete data set on acute rejections and the development of donor-specific antibodies during the study period was available.

6. Conclusion

In conclusion, our data indicate that the use of LCP-Tac after kidney transplantation in patients who have been switched from IR-tacrolimus was safe and led to stable trough levels in combination with further dose reduction one year after switch, and graft function was stable. This was

associated with good medication adherence.

Author contributions

LP and MS conceived and designed the study. LP drafted the study protocol. YS evaluated the data and performed the statistics. YS, and LP wrote the first draft of the paper. All authors read, revised, and approved the manuscript.

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Declaration of Competing Interest

This study received funding from Chiesi GmbH Germany. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication. All authors declare no other competing interests.

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