

Increased adherence eight months after switch from twice daily calcineurin inhibitor based treatment to once daily modified released tacrolimus in heart transplantation

Andreas O Doesch¹
Susanne Mueller¹
Ceylan Akyol¹
Christian Erbel¹
Lutz Frankenstein¹
Arjang Ruhparwar²
Philipp Ehlermann¹
Thomas J Dengler³
Hugo A Katus¹

¹Department of Cardiology, University of Heidelberg, Heidelberg, Germany;

²Department of Cardiovascular Surgery, University of Heidelberg, Heidelberg, Germany; ³Department of Cardiology, SLK-Kliniken Heilbronn, Bad Friedrichshall, Germany

Correspondence: Andreas O Doesch
Universitätsklinikum Heidelberg,
Medizinische Klinik III, Kardiologie,
Angiologie, Pulmologie, Im
Neuenheimer Feld 410, 69 120
Heidelberg, Germany
Tel +49 6221 5639936
Fax +49 6221 564105
Email andreas.doesch@med.uni-
heidelberg.de

Background: Modified-release tacrolimus (TAC) is a new, once-daily oral formulation of the established immunosuppressive agent TAC. This study evaluated long-term patient adherence, as well as safety and efficacy, in stable patients after heart transplantation (HTx) who switched from a conventional twice daily calcineurin inhibitor-based regimen (TAC or cyclosporine A [CsA]) to a once-daily modified-release TAC regimen.

Methods: Stable patients were switched from conventional TAC or CsA (twice-daily dosing) to modified-release TAC (once-daily dosing) according to manufacturer's recommendations using a pre-experimental design. Self-reported adherence was assessed at baseline and 8 months after the switch with the Basel Assessment of Adherence with Immunosuppressive Medication Scale (BAASIS). Additionally, routine laboratory values were analyzed 8 months after switch.

Results: Of 76 patients (58 male, 18 female) initially included, 72 were available for statistical analysis, as modified-release TAC was discontinued due to diarrhea in one patient and gastrointestinal discomfort in three patients. Overall nonadherence at baseline for any of the four BAASIS items was 75.0% versus 40.3% after 8 months ($P < 0.0001$). After 8 months, adherence was improved in 41 patients (56.9%), unchanged in 27 (37.5%), and reduced in four patients (5.6%). The BAASIS visual analog scale score improved significantly from $87.0\% \pm 13.5\%$ to $97.5\% \pm 5.7\%$ ($P < 0.0001$). No significant changes were observed for hematological, renal, or liver function parameters after 8 months (all $P =$ not significant).

Conclusion: To our knowledge, this is the first study in stable patients after HTx to demonstrate a significant improvement in long-term (ie, 8-month) patient adherence after the switch to modified-release TAC. Modified-release TAC was generally well tolerated. Further studies are currently underway to investigate long-term safety after HTx of various calcineurin inhibitors for prevention of rejection and occurrence of side effects.

Keywords: heart transplant, immunosuppression, modified-release tacrolimus, long-term adherence

Background

Modified-release tacrolimus (TAC) is a recently developed, once-daily oral formulation of the well-established immunosuppressive agent. Previous studies in patients treated with modified-release TAC after kidney or liver transplantation demonstrated comparable or favorable rates of postconversion patient and graft survivals, incidences of biopsy-proven acute rejection, multiple rejections, and safety profiles relative to conventional twice-daily TAC.¹⁻⁹ The modified and conventional TAC formulations show similar exposure (area under the curve) and trough levels (minimum concentration), with a

reduced peak level (maximum concentration).⁵ Long-term data on modified-release TAC in patients after heart transplant (HTx) are limited, however. Because lifelong immunosuppressive therapy is a necessity in this distinct patient cohort, the long-term cardiovascular side effects of immunosuppressive therapy cannot be underestimated.¹⁰ Additionally, simplification of dose regimens has been associated with improved adherence,¹¹ yet to our knowledge only short-term studies have evaluated the impact on adherence of switching patients from twice-daily to once-daily regimens after HTx.¹²

The aim of this follow-up analysis was to evaluate adherence levels after 8 months in stable patients post-HTx who were switched from a conventional twice-daily TAC or cyclosporine A (CsA) regimen to a once-daily modified-release TAC regimen. The interval of 8 months was chosen due to the routine follow-up protocol at the Heidelberg HTx center. A secondary aim was to evaluate tolerability, efficacy, and safety of modified-release TAC after the switch.

Methods

Design and sampling methods

Using a pre-experimental design, we included a convenience sample of patients seen at the Department of Cardiology, Heidelberg University Hospital, Germany between April 2009 and June 2012. Patients had to be at least 6 months post-HTx and free from acute infection or rejection for 4 months prior to study inclusion. Patients also had to be on stable doses of conventional TAC or CsA for 4 months preceding study entry (as part of a dual immunosuppressive regimen). Written informed consent was obtained prior to study entry. All human studies were reviewed and approved by the ethics committee of the University of Heidelberg. The setting in which this study was conducted has a compulsory health insurance system, and immunosuppressive medications are covered by the standard health insurance.

Intervention

Stable HTx recipients were switched from a twice-daily calcineurin inhibitor (conventional TAC/CsA) regimen to a single morning dose of modified-release TAC. Conversion to modified-release TAC was made from conventional TAC on a milligram-for-milligram basis and from CsA according to manufacturer's recommendations (Astellas Pharma GmbH, Munich, Germany). The oral dose of conventional or modified-release TAC was adjusted to reach target trough levels of 3–10 µg/L, depending on the amount of time since HTx. Alternatively, the oral dose of CsA was titrated to reach target trough levels of 50–140 µg/L, depending on the amount of time post-HTx.

Determinations of immunosuppressive medication trough levels were completed at entry (baseline visit), on day 7 postconversion, and thereafter every month postconversion or whenever clinically indicated (Figure 1). We applied the same therapeutic monitoring and patient-care techniques currently used with our CsA/TAC patients.

Variables and measurement

Demographic and clinical variables (Table 1) were retrieved from the patient's medical file. At baseline and the follow-up visit, routine laboratory (including doses and levels of immunosuppressive medication, blood count, and renal and liver function tests) and clinical assessments were obtained (according to the routine HTx follow-up protocol of the Department of Cardiology, Heidelberg University Hospital, Germany). Patients were asked (open question) to comment on the occurrence of side effects. Adherence with modified-release TAC was assessed by self-report using a validated adherence questionnaire, the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS).^{13,14} The BAASIS consists of four items measuring the taking and timing dimensions of medication taking, the presence of drug holidays, and dose reductions, along with a rating of overall adherence on a visual analog scale ranging from 0 (never took medications as prescribed) to 100 (always took medications as prescribed). The BAASIS is applied as an interview in which patients are asked in a nonaccusatory, information-intensive approach about their medication-taking behaviors. Self-reported adherence as measured by BAASIS was assessed at baseline and at 8 months after the switch to modified-release TAC. Nonadherence was defined

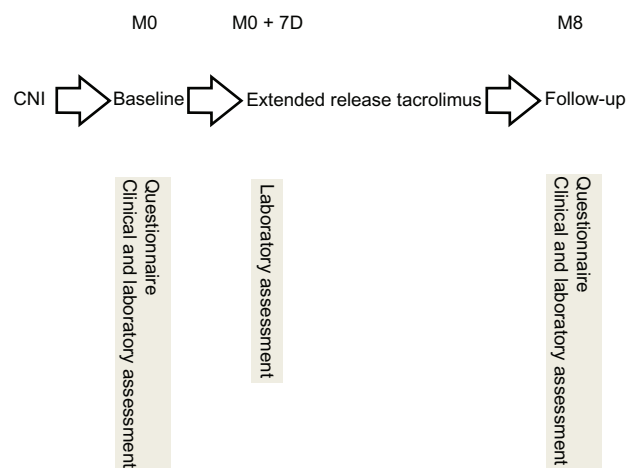


Figure 1 Pre-experimental design.

Notes: Timeline of study protocol. Seventy-two patients were available for statistical analysis due to discontinuation of modified-release tacrolimus in four patients.

Abbreviations: M, month; D, day; CNI, calcineurin inhibitor.

Table 1 Patient characteristics (n=76)

Parameter	Baseline		
Mean age (\pm SD, years)	46.0 \pm 14.4		
Mean time post HTx (\pm SD, years)	4.8 \pm 4.4		
Females (n, %)	18, 23.7		
Males (n, %)	58, 76.3		
Parameter (\pm SD)	Baseline (n=72)	Month 8 (n=72)	Level of significance
Hemoglobin (g/dL)	12.6 \pm 2.0	12.9 \pm 1.8	all <i>P</i> =NS
Leucocytes (/nL)	6.8 \pm 2.8	6.8 \pm 2.4	
Thrombocytes (/nL)	226.2 \pm 68.9	224.5 \pm 68.7	
GOT (units/L)	26.5 \pm 14.8	26.2 \pm 12.4	
GPT (units/L)	30.1 \pm 25.1	29.7 \pm 14.0	
GGT (units/L)	80.2 \pm 158.0	80.2 \pm 122.4	
Creatinine (mg/dL)	1.6 \pm 1.0	1.4 \pm 0.4	
Urea (mg/dL)	60.2 \pm 21.2	55.9 \pm 18.4	
Parameter (\pm SD)	Day 7 (n=72)	Month 8 (n=72)	Level of significance
Tacrolimus dose (mg/day)	4.5 \pm 3.0	3.9 \pm 2.1	<i>P</i> =0.003
Tacrolimus trough level (μ g/L)	6.5 \pm 1.8	6.3 \pm 2.0	<i>P</i> =NS

Abbreviations: n, number; SD, standard deviation; HTx, heart transplant; GOT, glutamate-oxaloacetate transaminase/aspartate transaminase; GPT, glutamate-pyruvate transaminase/alanine transaminase; GGT, gamma-glutamyl transferase; NS, not significant.

as any self-reported nonadherence on any of the four items. The presence of drug holidays or dose reductions was scored dichotomously (yes/no). The BAASIS' predictive validity has been shown in the HIV population with regard to viral rebound.¹⁵ Furthermore, the instrument showed fair diagnostic values, with sensitivity of 87.5% and specificity of 78.6%, when compared with prospective 1-year virologic failure in a sample of 133 patients with HIV.¹⁶

Statistical analysis

Variables were described using frequencies and mean \pm standard deviation as appropriate, on the basis of the measurement level and distribution. In order to compare the level of adherence before and after the switch, paired comparisons were performed using the McNemar test, paired *t* test, and Wilcoxon signed rank test for dichotomous, continuous normally distributed, and continuous not normally distributed variables, respectively. The level of significance was set at *P*<0.05. Statistical analyses were performed in SPSS (version 14.0, IBM Corporation, Armonk, NY, USA).

Results

Of 76 patients included in the study, 18 were women and 58 were men. The baseline immunosuppressive regimen for all 76 patients consisted of a calcineurin inhibitor (TAC [n=57] or CsA [n=19]) in combination with either mycophenolate mofetil (n=67), mTOR inhibitor (everolimus [n=7]), or azathioprine (n=2). The 57 patients receiving

conventional TAC were converted to modified-release TAC on a milligram-for-milligram (ie, 1:1) basis; the 19 patients receiving CsA were converted according to manufacturer's recommendations. Patient flow through the study is shown in Figure 1. Seventy-two patients were available for statistical analysis; four patients (5.3% of all patients included) were reinitiated on conventional TAC (n=3) or CsA (n=1) due to gastrointestinal discomfort (n=3) or diarrhea (n=1) and were not included in the analyses. Table 1 shows the demographic and clinical characteristics of the sample at baseline (n=72). Mean patient age was 46.0 \pm 14.4 years. Initial examination occurred 4.8 \pm 4.4 years after HTx (range 0.5–17.0 years post-HTx).

Adherence

Overall nonadherence at baseline for any of the four BAASIS items was 75.0%. For the subdimensions of taking and timing as well as the occurrence of drug holidays and dose reductions, the nonadherence levels were 33.3%, 69.4%, 0.0%, and 5.6%, respectively. After 8 months, overall nonadherence for any of the four items was 40.3% (*P*<0.0001). For the subdimensions of taking and timing as well as the occurrence of drug holidays and dose reductions, the nonadherence levels were 13.9% (*P*=0.0004), 30.6% (*P*<0.0001), 1.4% (*P*=NS), and 4.2% (*P*=NS), respectively. Overall nonadherence at baseline and after 8 months is depicted in Figure 2. After 8 months, adherence was improved in 41 patients (56.9% of total), unchanged in 27 patients (37.5% of total), and impaired in

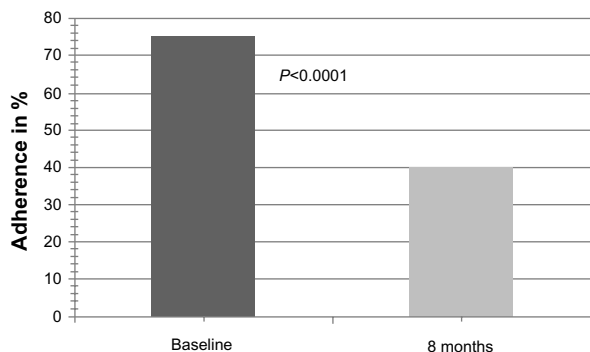


Figure 2 Overall self-reported adherence at baseline and 8 months after conversion to modified-release tacrolimus (BAASIS).

Note: Lower scores indicate better adherence.

Abbreviation: BAASIS, Basel Assessment of Adherence with Immunosuppressive Medication Scale.

four patients (5.6% of total). Similarly, the BAASIS visual analog scale score improved significantly from $87.0\% \pm 13.5\%$ to $97.5\% \pm 5.7\%$ ($P < 0.0001$, Figure 3).

Safety and tolerability

TAC doses/levels

Due to the time-dependent decrease in TAC target levels post-HTx, mean modified-release TAC dose was 3.9 ± 2.1 mg/day 8 months after the switch compared with 4.5 ± 3.0 mg/day on day 7 ($P = 0.003$, Figure 4A). Similarly, 8 months after the switch, mean modified-release TAC level was 6.3 ± 2.0 µg/L compared to 6.5 ± 1.8 µg/L on day 7 ($P = \text{NS}$, Figure 4B). After 7 days, 14 of 72 patients (19.4% of total) were not within the range of target levels. Of these 14 patients, only six patients (8.3% of total) had a TAC trough level differing more than 1 µg/L from target level. These patients included one patient initially on CsA and five patients on TAC.

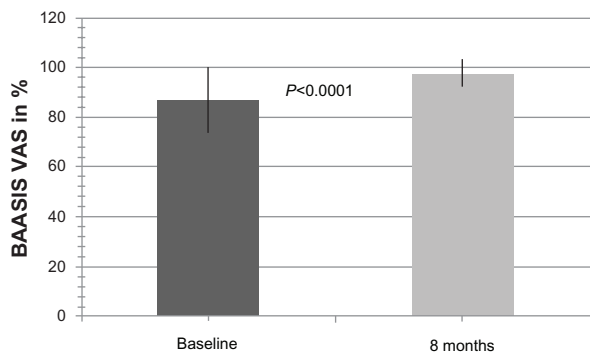


Figure 3 Overall self-reported adherence at baseline and 8 months after conversion to modified-release tacrolimus (BAASIS-VAS scale).

Notes: Scores are \pm standard deviation. Higher scores indicate better adherence.

Abbreviations: BAASIS, Basel Assessment of Adherence with Immunosuppressive Medication Scale; VAS, visual analog scale.

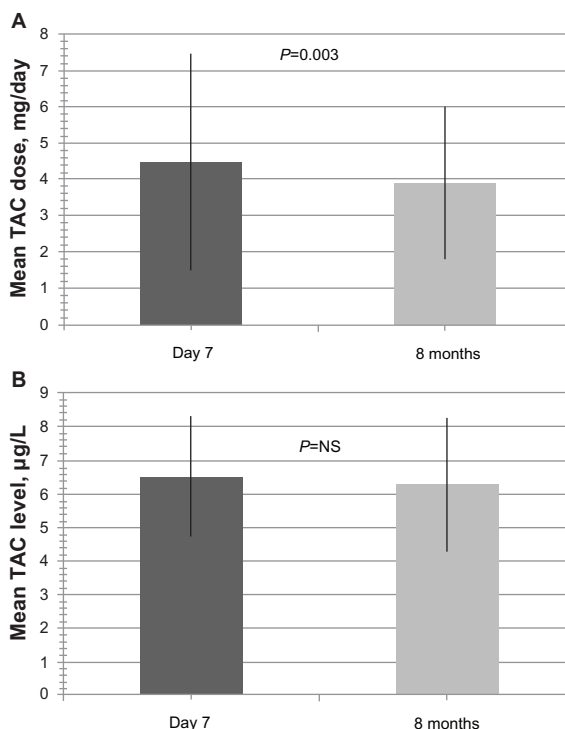


Figure 4 Modified-release tacrolimus doses and levels at day 7 and month 8 after conversion to modified-release tacrolimus.

Notes: (A) Mean daily modified-release TAC dose (mg) (\pm standard deviation) 7 days and 8 months after conversion. (B) Mean modified-release TAC level (µg/L) (\pm standard deviation) 7 days and 8 months after conversion.

Abbreviation: TAC, tacrolimus.

Routine laboratory parameters

Serum creatinine levels remained stable after conversion to modified-release TAC. The baseline value for serum creatinine was 1.6 ± 1.0 mg/dL, and the value at month 8 was 1.4 ± 0.4 mg/dL ($P = \text{not significant [NS]}$; Table 1). In addition, no significant changes were observed in hematologic and liver function parameters (all $P = \text{NS}$, Table 1). No cases of acute rejection were found during the study period.

Side effects

Four patients (5.3% of all patients included) were reintiated on conventional TAC ($n = 3$) or CsA ($n = 1$) due to gastrointestinal discomfort ($n = 3$) and diarrhea ($n = 1$). Symptoms were self limiting after switch, serologic parameters were within normal limits, and microbiological testing was negative.

Discussion

Adherence

In patients after HTx, our follow-up study showed a significant adherence improvement after switch to a single daily dose of modified-release TAC, which can be attributed to

more timely immunosuppression and fewer skipped single doses. No significant changes in occurrence of independent reduction of doses was observed, which is not surprising due to the vital importance of immunosuppression after HTx. However, a slight increase in the occurrence of multiple skipped doses (drug holidays) was observed but did not reach the level of statistical significance. Admittedly, given the single-center study design, these results need to be interpreted conservatively.

Safety and tolerability

TAC has gained widespread acceptance as part of a dual immunosuppressive regimen and has proven to be effective in preventing allograft rejection after HTx.^{17,18} Modified-release TAC is very similar to conventional TAC in terms of bioavailability, but due to its prolonged-release formula with one single daily dose it has several advantages. Generally, the switch to modified-release TAC was feasible, effective, and safe. After 7 days, most patients were within target levels, irrespective of the initial calcineurin inhibitor. Modified-release TAC was generally well tolerated. No serious adverse events were noticed during the study. In four patients the initial calcineurin inhibitor had to be reinitiated, mainly due to gastrointestinal symptoms, which were generally mild and self-limiting.

No statistically significant changes in hematologic, liver, or renal function parameters were observed after the switch to modified-release TAC. Our study showed that mean TAC trough levels decreased during the course of the study. However, as several patients were included during the first year post-HTx, this is not unexpected, as TAC target levels were continuously adapted after HTx according to our center's routine regimen. Patients maintained effective immunosuppression during the entire study period; there were no cases of biopsy-confirmed acute rejection during the treatment period.

Limitations of the study

To our knowledge, this is the first study reporting on improved adherence in patients after heart transplant 8 months after the switch from a conventional calcineurin inhibitor (twice-daily TAC or CsA) to once-daily modified-release TAC. Admittedly using a pre-experimental design, this study nevertheless provides important information on relevant clinical parameters related to adherence, safety, and the tolerability of switching patients, and it confirms findings from the literature that simplification of dosing regimen does result in improved adherence.¹⁹

Conclusion

Therapeutic regimens for transplant recipients are often complex and become a limiting factor for medication adherence. This study in stable patients after HTx suggests a significant improvement in patient adherence after switch to modified-release TAC, in line with previously published short-term data.¹² Modified-release TAC was generally well tolerated. On the basis of the given data, we conclude that switching to modified-release TAC from a conventional calcineurin inhibitor is generally feasible, effective, and safe. Further studies are currently underway to investigate long-term safety and side effects in patients taking conventional TAC, extended-release TAC, or CsA after HTx.

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Disclosure

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