

## Influence of tacrolimus metabolism rate on renal function after solid organ transplantation

Gerold Thölking, Hans Ulrich Gerth, Katharina Schuette-Nuetgen, Stefan Reuter

Gerold Thölking, Hans Ulrich Gerth, Katharina Schuette-Nuetgen, Stefan Reuter, Division of General Internal Medicine, Nephrology and Rheumatology, Department of Medicine D, University Hospital of Münster, 48149 Münster, Germany

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**Correspondence to:** Gerold Thölking, MD, Division of General Internal Medicine, Nephrology and Rheumatology, Department of Medicine D, University Hospital of Münster, Albert-Schweitzer-Campus 1, Gebäude A1, 48149 Münster, Germany. [gerold.thoelking@ukmuenster.de](mailto:gerold.thoelking@ukmuenster.de)  
Telephone: +49-251-8348001  
Fax: +49-251-8346979

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### Abstract

The calcineurin inhibitor (CNI) tacrolimus (TAC) is an integral part of the immunosuppressive regimen after solid organ transplantation. Although TAC is very effective in prevention of acute rejection episodes, its highly variable pharmacokinetic and narrow therapeutic window require frequent monitoring of drug levels and dose adjustments. TAC can cause CNI nephrotoxicity even at low blood trough levels (4-6 ng/mL). Thus, other factors besides the TAC trough level might contribute to CNI-related kidney injury. Unfortunately, TAC pharmacokinetic is determined by a whole bunch of parameters. However, for daily clinical routine a simple application strategy is needed. To address this problem, we and others have evaluated a simple calculation method in which the TAC blood trough concentration (C) is divided by the daily dose (D). Fast TAC metabolism (C/D ratio < 1.05) was identified as a potential risk factor for an inferior kidney function after transplantation. In this regard, we recently showed a strong association between fast TAC metabolism and CNI nephrotoxicity as well as BKV infection. Therefore, the TAC C/D ratio may assist transplant clinicians in a simple way to individualize the immunosuppressive regimen.

**Key words:** Tacrolimus; Liver; Metabolism; Transplantation; Kidney

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**Core tip:** The calcineurin inhibitor tacrolimus (TAC) is the mainstay of the immunosuppressive regimen after solid organ transplantation. Nevertheless, TAC can cause nephrotoxicity even at low blood trough levels. Thus, other factors than the TAC trough level might be responsible for kidney injury. Recently published studies showed a strong association between fast TAC metabolism and nephrotoxicity as well as BK virus infection. The TAC

metabolism rate defined as the TAC concentration/dose ratio is a cost neutral tool to identify patients at risk for TAC-associated decline in renal function after transplantation.

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## INTRODUCTION

The calcineurin inhibitor (CNI) tacrolimus (TAC) is a cornerstone of the immunosuppressive regimen after solid organ transplantation. Nevertheless, its highly variable pharmacokinetics and narrow therapeutic window require frequent therapeutic drug monitoring (TDM) and the (nephrotoxic) side effects of TAC might limit its application<sup>[1]</sup>. In particular dose adjustment after TAC prescription is difficult as many patients often show troughs above or below their target range despite TDM. In order to overcome these limitations, new TAC formulations with different galenics have been developed and different protocols with TAC dose reduction, switch, elimination and combination of reduced TAC and mechanistic target of rapamycin (mTOR) inhibitors have been studied<sup>[2-5]</sup>. *E.g.*, the recent ATHENA trial evaluates a *de novo* everolimus (EVR)-based regimen in combination with reduced cyclosporine A (CSA) or TAC vs a standard regimen in patients that underwent renal transplantation (RTx)<sup>[6]</sup>. Results of this trial are expected soon.

After RTx, low dosed TAC regimens showed superiority regarding the prevention of biopsy-proven acute rejection (BPAR) and preserving the kidney function compared to the CNI CSA and the mTOR inhibitor sirolimus (SRL)<sup>[7,8]</sup>. Consistently, the present KDIGO guideline recommends TAC-based immunosuppression after RTx<sup>[9]</sup>.

TAC has also become a first choice immunosuppressive drug after liver transplantation (LTx)<sup>[10]</sup>. Compared to CSA, TAC-treated patients - though experiencing a higher rate of posttransplant diabetes mellitus - showed a significantly reduced mortality at 1- and 3-years post-transplant; rates of graft loss and (steroid-resistant) rejection were lower in these patients<sup>[11,12]</sup>. In order to avoid CNI nephrotoxicity in LTx patients, several studies have been conducted to evaluate treatment strategies in which standard dosed TAC was either replaced by low dose TAC and mTOR inhibitor or CNI were even completely eliminated from the regimen. In a study with 78 LTx patients renal function recovered slightly after conversion from TAC to an mTOR inhibitor-based regimen<sup>[13]</sup>. Immunosuppression was switched 31 mo (median) after LTx. Additionally, Fischer *et al.*<sup>[14]</sup> showed in a prospective, multicenter, open-label study with *de novo* LTx patients that patients who were randomized to regimen with reduced TAC dose and EVR

30 d after LTx developed lower rates of BPAR and had an improved renal function from randomization to month 36 compared to patients with standard TAC doses. Of note, randomization to the TAC elimination arm in this study was stopped prematurely due to significant higher BPAR rates<sup>[15]</sup>.

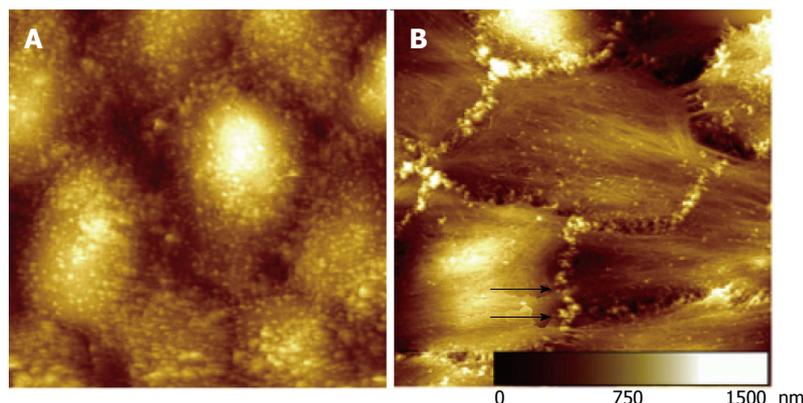
In pancreas, heart, lung, or combined organ transplantation, TAC also constitutes an integral part of the immunosuppressive regimen<sup>[16-20]</sup>. CNI-sparing or -free regimens in these patients are currently investigated but safety of these concepts is still under debate. Notably, none of these CNI-free regimens has yet been shown to provide an immunosuppressive efficacy that equals those of CNIs<sup>[21-23]</sup>.

After pancreas transplantation TAC and mycophenolate mofetil (MMF) maintenance therapy seems to be the most effective immunosuppressive regimen with regard to long term survival and prevention of acute rejection<sup>[16,24]</sup>. However, occurrence of TAC-related side effects like posttransplant diabetes mellitus or nephrotoxicity has led to increasing efforts to minimize CNI in this cohort. *E.g.*, in one study pancreas transplanted patients were switched from standard immunosuppression with TAC and MMF to low dose TAC and SRL<sup>[25]</sup>. From the authors view, the low dose TAC and SRL regimen was safe and did not worsen proteinuria and renal function when compared with TAC and MMF. In simultaneous pancreas and kidney transplantation Sageshima *et al.*<sup>[17]</sup> evaluated the efficacy and safety of TAC and EVR compared to TAC and MMF in a retrospective study. Unfortunately, both studies failed to show relevant advantages of the combined TAC/mTOR regimen.

The introduction of EVR in the maintenance therapy of heart transplant recipients, with reduced CNI, has been shown to significantly improve the renal function during an observational period of at least 5 years<sup>[18]</sup>. An early renal benefit in lung transplant recipients was lost over the time but long-term immunosuppressive efficacy was maintained<sup>[18]</sup>.

Despite all efforts to minimize TAC exposure and its side effects even in low dose regimens (4-6 ng/mL)<sup>[26]</sup>, TAC, however, remains the mainstay of the immunosuppressive regimen after solid organ transplantation<sup>[2,14]</sup>. Therefore, transplant physicians need an approach to identify patients at risk to develop TAC-related side effects in clinical routine. We and others proposed that the patient's individual TAC metabolism type can be used for adaption of the immunosuppressive regimen. We believe that the TAC metabolism rate defined as the TAC blood trough concentration (C) divided by the daily dose (D) is such a convenient predictor for TAC metabolism estimation. Perspectively, C/D tests could probably detect patients at high risk of developing TAC-related complications even before their transplantation.

Due to missing data on the TAC metabolism rate and its value in recipients of other organ transplants than kidney and liver, we herein focus on the impact of the C/D ratio in the latter.



**Figure 1 Morphological changes of cells undergoing epithelial to mesenchymal transformation.** Images from atomic force microscopy of glutaraldehyde fixed cells in fluid (highest sample areas are represented in white). A: Typically, epithelial tubular cells (NRK-52E), ( $50\ \mu\text{m}$ )<sup>2</sup>, appear with numerous microvilli compatible structures on the cellular surface; B: Tubular cells after six days of TGF- $\beta$ 1 treatment ( $50\ \mu\text{m}$ )<sup>2</sup>. Cells show a fibrillary surface structure with rarefied microvilli. Nodular protrusions developed at the cell borders (black arrows)<sup>[35]</sup>. ©IOP Publishing. Reproduced with permission. All rights reserved. TGF: Transforming growth factor.

## HISTOLOGICAL MANIFESTATION OF CNI-NEPHROTOXICITY

TAC has a narrow therapeutic window and can cause acute and chronic nephrotoxicity. However, some authors even question the concept of a “harmless” therapeutic window. They state that yet to be effective, CNI must operate within their nephrotoxic therapeutic range as can be seen when CNI withdrawal leads to an immediate increase in estimated glomerular filtration rate (eGFR)<sup>[1]</sup>. Activation of the renin-angiotensin system and increased sympathetic nerve activity causing vasospasm of renal arteries might be involved in this context<sup>[27,28]</sup>. An imbalance of vasodilatory factors like nitric oxide<sup>[29,30]</sup> and prostaglandins<sup>[30]</sup> and vasoconstrictive variables like thromboxane<sup>[31]</sup> and endothelin<sup>[32]</sup> is discussed to promote further renal damage.

Acute CNI nephrotoxicity typically appears early after RTx correlating to the period of high CNI exposure. It presents, *e.g.*, with acute arteriopathy, tubular vacuolization and swelling of endothelial cells and death of myocytes of the tunica media<sup>[1]</sup>. The prevalence of CNI-associated chronic lesions increases by time<sup>[1]</sup>.

Tubule-interstitial fibrosis/tubular atrophy (IF/TA) is a typical histological finding in chronic CNI-related allograft injury. Tubular microcalcifications, glomerulosclerosis and arteriolar hyalinosis are further chronic manifestations. In contrast to some acute CNI-related kidney injuries which can be resolved within the first months after RTx, chronic CNI-nephrotoxicity observed after the third month after RTx is usually progressive<sup>[1]</sup>.

For example, TAC exposure induces epithelial-mesenchymal transition (EMT) by activation of the profibrotic cytokine transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) pathway in renal tubular cells<sup>[33]</sup>. TGF- $\beta$ 1 in turn induces cell growth, increases the production of smooth-muscle actin and stress fiber formation in epithelial cells<sup>[33,34]</sup>. This results in a decrease of cellular surface microvilli and increases stiffness of tubular epithelial cells<sup>[35]</sup>. During this conversion process, tubular cells lose epithelial characteristics and appear in a mesenchymal shape (Figure 1<sup>[35]</sup>) (EMT). However, these effects seem to be cell specific. While some cells have the ability to proliferate, others are decomposed by autophagy<sup>[33,36]</sup>.

Early withdrawal or dose reduction of TAC/CNI and introduction of an mTOR inhibitor might stabilize fibrosis<sup>[37]</sup>. However, the adequate time point for TAC/CNI withdrawal or dose reduction is still elusive and the group of patients who might benefit from this intervention remains yet to be clearly identified<sup>[2,3,13,14,38]</sup>.

## INFLUENCES ON TACROLIMUS METABOLISM

TAC metabolism underlies several individual, genetic and clinical, as well as pharmacokinetic factors. Recipient age, gender, body mass index, delayed graft function, hematocrit, serum albumin and absorption have been proposed to be relevant determinants<sup>[39-42]</sup>. However, some of these factors are still a matter of debate.

Drug interactions interfering with TAC metabolism are of high clinical relevance for physicians. Changes of the TAC pharmacokinetic by other immunosuppressive drugs, such as EVR, SRL and corticosteroids have to be considered in daily routine. Especially, induction of TAC metabolism by high doses of corticosteroids has to be taken into account early after transplantation<sup>[40,41,43]</sup>. Whether these interactions are of clinical relevance or not remains largely unknown<sup>[44]</sup>.

TAC metabolism is influenced by cytochrome-P450 enzymes *CYP3A* expression variants, *e.g.*, in the intestine<sup>[45,46]</sup>. This genetic expression variant determines the first-pass effect of orally administered TAC. This is important, because Sato *et al.*<sup>[47]</sup> showed that recipients taking their usual dose of TAC in case of diarrhea had significant elevated trough levels and a prolongation of maximum concentrations when compared to the regular situation. It is supposed, that this phenomenon is caused by a shift of the main intestinal areas of TAC metabolism (duodenum and jejunum) to the lower intestine<sup>[47,48]</sup>.

The *CYP3A4* and *CYP3A5* variants in the liver lead to significant differences in TAC pharmacokinetics<sup>[39,41,49]</sup>. Predominantly but not exclusively, *CYP3A5\*1*-expressors have been characterized as fast TAC metabolizers, while slow metabolizers mostly express *CYP3A5\*3*<sup>[45,50-52]</sup>. Early after transplantation, it has been shown that a rapid decline in TAC metabolism is only present in *CYP3A5\*3/\*3* patients while the decline is absent in *CYP3A5\*1* allele

carriers<sup>[53,54]</sup>. This finding might be explained by high steroid doses and a gradual rise in hematocrit that affect *CYP3A5\*3/\*3* and *CYP3A4* activity. In comparison, *CYP3A5* carriers (*CYP3A5\*1*) receive higher TAC doses (fast metabolizers) early after transplantation and continue with a higher or even increased exposure as time after transplantation elapses<sup>[41]</sup>. In a meta-analysis, Shi *et al*<sup>[55]</sup> showed that especially *CYP3A4\*1B* genetic polymorphism may affect TAC metabolism. If the presence of *CYP3A5* in the kidney, *i.e.*, in the renal apical tubular plasma membrane impacts, *e.g.*, on the degree of CNI nephrotoxicity is still a matter of debate<sup>[56,57]</sup>.

Unfortunately, the dosage needed to achieve the target TAC level varies in patients with known *CYP3A* polymorphisms over time<sup>[58]</sup>. Therefore, genetic testing does not solve the dosing problem and we still have to rely on trough level testing. To end this, genotyping of patients is still far from being a routine test and at present of questionable relevance in the daily transplant setting.

## CLINICAL IMPACT OF TAC METABOLISM RATE

The TAC concentration/dose ratio (C/D ratio) is an established equation to describe the TAC metabolism rate<sup>[59-61]</sup>:  $C/D \text{ ratio (ng/mL} \cdot 1/\text{mg)} = [\text{Blood TAC trough concentration (ng/mL)}]/[\text{Daily TAC dose (mg)}]$ .

We intended to keep the approach very simple and tested if body weight (which was suggested to be included into the equation by others) can be removed from the equation<sup>[59,60,62]</sup>. Our approach was supported by Kim *et al*<sup>[58]</sup> who showed that TAC adverse events in a 5-year follow-up of RTx patients were independent from body weight.

The presented equation provides a simple, cost neutral clinical tool which can be applied without performing additional tests. Standard trough levels from regular therapeutic TAC drug monitoring can be used for C/D ratio calculation of in- as well as outpatients.

We analyzed TAC metabolism using the C/D ratio in a study of 248 RTx patients at our center. Analyzing the outcomes and distribution of recipients' C/D ratios in our cohort, we calculated a cut off for the TAC C/D ratio of 1.05 for definition of fast metabolizers. After a 24 mo follow-up, patients with a C/D ratio < 1.05 had a lower eGFR, needed more indication biopsies and showed more often biopsy proven CNI nephrotoxicity compared to intermediate and slow TAC metabolizers<sup>[60]</sup>. In accordance with our data, Kuypers *et al*<sup>[63]</sup> showed that *CYP3A5\*1* genotype carriers (mainly fast metabolizers) had a significantly increased risk for biopsy-proven TAC-induced nephrotoxicity [HR: 2.38 (1.15-4.92),  $P = 0.01$ ] at 3 mo post-transplant. These results were confirmed by Genvigir *et al*<sup>[64]</sup> who also reported that carriage of two or more fast metabolism *CYP3A5* alleles is associated with lower eGFR values ninety days after RTx. Rojas *et al*<sup>[65]</sup> showed that the weight adjusted C/D ratio in RTx recipients among

*CYP3A5\*1* allele carriers compared with carriers of the *CYP3A5\*3/\*3* genotype was lower and demonstrated that the expresser genotype was associated with a higher risk of acute rejection and chronic nephrotoxicity. Nevertheless, further studies on similar and different ethnical cohorts showed partly contradictory results<sup>[66-68]</sup>. Thus, until now, the prediction of renal function by *CYP3A* genotyping still remains ambiguous.

We confirmed our findings in a cohort of LTx patients. During a 36 mo follow-up renal function was lower in fast TAC metabolizers (defined by C/D ratio) than in slow TAC metabolizers (Figure 2)<sup>[59]</sup>. In this study, fast metabolizers had more TAC side effects like higher rates of assumed CNI nephrotoxicity and had been more often switched from TAC to other immunosuppressive drugs.

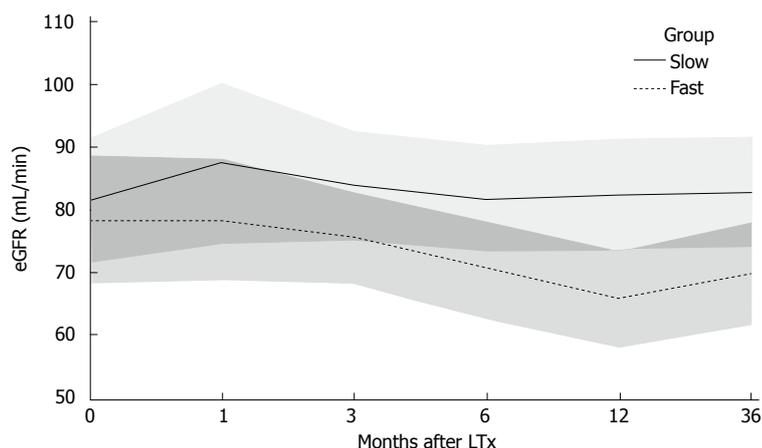
It is well known that higher TAC trough levels are more toxic and increase the risk of side effects<sup>[69]</sup>. Jacobson *et al* for example calculated a HR of 1.22 for a 1 ng/mL increase of the TAC trough level to develop acute CNI nephrotoxicity after RTx. It is important to note that our RTx patients in the fast metabolizer cohort had lower TAC trough levels at 1, 3 and 6 mo after transplantation compared to slower metabolizers (Table 1<sup>[60]</sup>). This was confirmed in a cohort of LTx patients<sup>[59]</sup>. Kuypers *et al*<sup>[63]</sup> identified nephrotoxicity to be dependent on the TAC dose. In accordance to these results, in our studies fast metabolizers received higher TAC doses than slow metabolizers 1, 3 and 6 mo after transplantation<sup>[59,60]</sup>. These findings led us to the hypothesis that CNI nephropathy predominantly seen in fast metabolizers might be related to TAC overexposure during the first hours after TAC intake.

This hypothesis is supported by the finding that besides increased rates of CNI nephrotoxicity, a higher incidence of BKV nephropathy (BKN) is observed in fast TAC metabolizers<sup>[60]</sup>. This was confirmed in a second study involving 192 RTx patients (96 BKV positive and 96 BKV negative controls). Patients with BKV infection showed lower Tac C/D ratios at 1, 3 and 6 mo after RTx and were mainly classified as fast TAC metabolizers<sup>[62]</sup>. Therefore, fast TAC metabolizers seem to be prone to CNI nephrotoxicity and suffer more likely from BKV infection<sup>[70]</sup>.

## SUMMARY

Although TAC is a cornerstone in the immunosuppressive regimen after solid organ transplantation, nephrotoxic site effects and a narrow therapeutic window may limit its application. Elimination, dose reduction, or replacement of TAC is often foiled by increased rates of BPAR<sup>[14,38]</sup>, occurrence of adverse events<sup>[8]</sup> or considerable rise in the costs caused by replacing immunosuppressive drugs like belatacept<sup>[71]</sup>. Due to the fact, that CNI nephrotoxicity can also occur in regimens with low TAC target levels<sup>[26]</sup>, a tool to identify patients at risk for developing an inferior kidney function is desirable.

We were able to demonstrate a strong association between a low TAC C/D ratio (< 1.05 ng/mL\*1/mg) and



**Figure 2** Estimated renal function measured by estimated glomerular filtration rate (Cockcroft-Gault eGFR, mL/min) after liver transplantation. There was no noticeable difference between fast and slow tacrolimus metabolizers at liver transplantation at 1 mo or 3 mo after liver transplantation. After 6, 12, and 36 mo, slow tacrolimus metabolizers had a significantly better renal function than fast metabolizers. Mean estimates and corresponding 95% confidence intervals from the multivariable linear mixed model are plotted; overlapping areas are shown in dark grey<sup>[59]</sup>. eGFR: Estimated glomerular filtration rate.

**Table 1 Medication doses and blood trough concentrations**

	Fast metabolizers (n = 97)	Interm metabolizers (n = 78)	Slow metabolizers (n = 73)	P value
Tacrolimus mean trough level (ng/mL)	8.2 ± 1.6	9.2 ± 1.8	9.5 ± 1.8	< 0.001 <sup>a</sup>
After 1 mo	9.4 ± 3.2	10.5 ± 2.7	11.0 ± 3.2	0.002 <sup>a</sup>
After 3 mo	7.8 ± 2.1	9.1 ± 2.9	9.5 ± 2.8	< 0.001 <sup>a</sup>
After 6 mo	7.2 ± 2.3	7.8 ± 2.4	8.0 ± 2.8	0.079 <sup>a</sup>
Tacrolimus mean daily dose (mg)	11 (6-27)	8 (4-14)	6 (2-12)	< 0.001 <sup>b</sup>
After 1 mo	14 (6-40)	10 (4-22)	8 (2-20)	< 0.001 <sup>b</sup>
After 3 mo	10 (4-23)	7 (4-13)	4 (2-12)	< 0.001 <sup>b</sup>
After 6 mo	9 (3-21)	5 (2-10)	3 (2-8)	< 0.001 <sup>b</sup>
Prednisolon mean daily dose (mg)	15 (4-37)	14 (5-70)	13 (0-40)	0.06 <sup>b</sup>
After 1 mo	20 (15-90)	20 (15-70)	20 (0-50)	0.155 <sup>b</sup>
After 3 mo	14 (3-30)	13 (5-30)	13 (0-30)	0.496 <sup>b</sup>
After 6 mo	10 (5-30)	9 (5-20)	8 (0-20)	0.114 <sup>b</sup>

Tacrolimus (TAC) trough levels and doses and prednisolone doses after renal transplantation. Fast metabolizers revealed noticeable lower TAC trough levels but higher TAC doses compared to intermediate and slow metabolizers. Prednisolone doses did not differ noticeably between the groups. <sup>a</sup>P-value is from the one-way ANOVA; <sup>b</sup>P-value is from the Kruskal-Wallis test; interm., intermediate; modified according to Thölkling *et al*<sup>[60]</sup>.

reduced renal function after a follow-up of 24 and 36 mo after RTx and LTx, respectively<sup>[59,60]</sup>. Furthermore, a low C/D ratio (fast TAC metabolism) led to more indication biopsies, more CNI nephrotoxicity and more BKV infection after RTx<sup>[62]</sup>.

In this context, *CYP3A* genotyping has improved our knowledge on TAC metabolism and might explain why patients present as slow or fast metabolizers but its predictive value in terms of TAC dose requirement or renal function is still unsatisfactory<sup>[58]</sup>. Currently, genetic testing does not deliver relevant data and counteracts our simplification strategy in the daily routine.

## CONCLUSION

In conclusion, fast TAC metabolism is associated with a reduced renal function after RTx and LTx. Higher rates of CNI nephrotoxicity and BKV infections/BKVN are assumed to be at least partly responsible for these results. Calculation of the TAC C/D ratio is a simple clinical tool that may assist transplant clinicians in individualizing immunosuppressive regimens.

Controlled, prospective, multicenter trials are needed to confirm the predictive value of the TAC C/D ratio.

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