Guidelines

TACROLIMUS THERAPEUTIC DRUG MONITORING

Updated September 3, 2021

TABLE OF CONTENTS

ABBREVIATIONS

AUC	area under the concentration curve
$AUC_{0\text{-}12h}$	area under the concentration curve for a 12 h study (from hour 0 to 12)
C0	concentration at time zero (pre-dose)
CV	coefficient of variance
IS	immunosuppressant
LLTR	lower limit of target range
MMF	mycophenolate mofetil (a.k.a. CellCept)
MPA	mycophenolic acid (a.k.a. mycophenolate), the active molecule in MMF and MPS
MPS	mycophenolate sodium (a.k.a. Myfortic)
PK	pharmacokinetics (pharmacokinetic studies)
r^2	correlation coefficient
SD	standard deviation
TAC	tacrolimus
TCMR	T cell-mediated rejection
TDM	therapeutic drug monitoring
ULTR	upper limit of target range

GUIDING PRINCIPLES

Therapeutic drug monitoring is required to optimize drug exposure for tacrolimus-based primary immunosuppression. Drug dosage is not reliable for prediction of drug exposure, due to variability of drug metabolism between individuals and with development. Trough level therapeutic drug monitoring (TDM) is therefore used clinically for monitoring of tacrolimus exposure.

- The primary measure of drug exposure is area-under-the-concentration curve (AUC). Since measurement requires pharmacokinetic studies, trough level (C0) is used as a surrogate marker of drug exposure, since it shows adequate correlation with AUC.
- The goal of treatment is to achieve a desired target of drug exposure (AUC), and this is estimated by achieving C0 within a given range by regular TDM.
- Tacrolimus targets are determined by stage after transplant and individualized according to assessed risk of rejection.
- Reliable TDM requires measurement of trough drug levels within a window of 11-13 hours after the last drug dose taken (23-25 hours for extended-release tacrolimus).
- Under-exposure to tacrolimus is considered a major risk for rejection, and therefore low drug levels are considered a greater patient risk than high drug levels
- Excessive over-correction is avoided by requiring persistent low/high drug levels within a limited tolerance before making dose corrections
- Dose correction is generally limited to +/- 10-15% of the previous dose for routine monitoring, unless there is a specific reason to justify larger dose changes.
- Increase of drug dosage because of low trough levels requires verification of the new trough level, to ensure adequate drug exposure on the new dose.

TACROLIMUS TDM GUIDELINES

RISK ASSESSMENT

1. New transplant
    - The risk of rejection is increased in all transplant recipients in the first 3-6 months post-transplantation, and therefore higher trough levels are targeted in the early post-transplant period.
    - In patients identified as being at increased risk for rejection at the time of transplantation, higher trough levels may be targeted.

2. Acute rejection
    - Increased tacrolimus exposure is prescribed as part of the standard treatment of acute TCMR, which is achieved by increasing the target trough level.

3. Corticosteroid interactions
    - In patients not already on steroids, induction with high dose IV methylprednisolone results in a temporary **inhibition** of tacrolimus metabolism. This results in a temporary **increase in tacrolimus level** that lasts 48-72 hours, for a given dose of tacrolimus.
    - With continued exposure, both methylprednisolone and prednisone both cause **induction** of tacrolimus metabolism resulting in increased drug clearance, and progressively **lower tacrolimus levels** on the same dose.
    - In the first 48-72 hours post-transplant, tacrolimus dosing should be guided by dose recommendations and high levels (>15) should be ignored in this time period unless there is evidence for tacrolimus toxicity (e.g. rising Cr).
    - In the setting of **low tacrolimus level during the first 72 hours** (below target), drug dose should be increased in proportion to the deficit to achieve minimum therapeutic drug exposure.
    - <u>As steroid dose is tapered over weeks/months post-transplant, tacrolimus metabolism is less rapid (as steroid-induced induction is reduced) and tacrolimus levels may slowly rise while on the same dose.</u> In this setting, drug dose should be adjusted periodically to compensate to achieve the intended drug exposure target (1-5).

4. Non-adherence and increased trough level variability
    - High variability in the tacrolimus trough level on repeated measures with the same dose may signal inconsistent drug exposure.
    - Non-adherence to treatment is a common cause of high trough-level variability and should be investigated
    - Food intake at the time of medication administration reduces drug absorption. Inconsistent timing of meals in relation to medication times will result in increased variability of drug exposure.
    - Some medications may affect drug metabolism of tacrolimus resulting in increased or decreased drug exposure.
    - Gastrointestinal disease can affect (decrease) the first pass metabolism of tacrolimus resulting in increased drug exposure and higher trough levels.

5. Hospitalization or other acute illness

- Beyond specific risks associated with gastrointestinal metabolism, drug requirements may change due to differences in food intake, hydration, hepatic dysfunction, medication changes, etc.
    i. Diarrheal illness associated with small bowel enterocyte injury (such as infectious diarrhea) may be associated with reduced first-pass tacrolimus metabolism resulting in increased drug absorption, and more elevated tacrolimus levels.
    ii. Reduced intake of food or NPO (especially when tacrolimus is normally taken with food) may be associated with increase drug availability and absorption, and more elevated tacrolimus levels.
    iii. Many different medications can affect tacrolimus metabolism, resulting in either increased or decreased drug exposure during the treatment period.
    iv. In the setting of acute kidney injury (AKI), unless the tacrolimus level is at supratherapeutic level, the dose of tacrolimus should NOT be empirically reduced due to an increased risk for rejection and absence of evidence for benefit.
    v. In the setting of acute electrolyte disturbance (e.g. hypomagnesemia or hyperkalemia), unless the tacrolimus level is at supratherapeutic level, the dose of tacrolimus should NOT be empirically reduced due to an increased risk for rejection and absence of evidence for benefit.
- Drug requirements for tacrolimus to maintain targeted drug exposure are expected to return to baseline (prior to the illness), following resolution of acute illness. Dosing changes made with an acute illness should be reviewed as illness resolves, with the bias toward resuming the previous tacrolimus dosing unless there is a reason to expect that a more lasting change in drug metabolism will persist beyond the acute illness period.
- TDM should be repeated within 1-2 weeks after hospital discharge, to verify that drug metabolism has returned to baseline and that drug exposure remains within the specified target range.
-

6. Growth and change in body mass
    - With increased body mass due to either obesity or normal growth, drug requirements are expected to increase
    - Drug metabolism changes with stage of development resulting in changing dosage requirements at different developmental stages.
    - Drug metabolism rate for tacrolimus gradually decreases during adolescence, such that dosage requirements may decline in early/mid adolescence.

7. Variation in drug pharmacokinetics (PK)
    - At the best of times, correlation between C0 (trough) and AUC in pediatric transplant recipients is in the range of r^2 = 0.36-0.84. This means that trough drug levels do not always accurately predict drug exposure, which may result in increased risk of rejection or inadvertent drug toxicity.
    - The relationship of C0 trough level to AUC is linear, with the usual ratio of drug trough level to AUC in the range of 1:15 to 1:16.
    - In younger children, the relationship of C0 to AUC is tighter (ratio ~1:15) and children tend to need increased dosage to achieve similar drug exposure as older children.
    - Corticosteroid use is associated with a higher AUC for a give C0 (ratio ~1:17), and poorer overall correlation with AUC (r^2=0.5), compared with patients not receiving steroids (r^2>0.9).

- The relationship of time post-transplant to PK changes is unclear, independent of changes that may occur related to corticosteroid use.
- Generally once a stable dose for treatment is achieved, the PK profile remains similar and predictable for a given patient on a given dosage.

8. Genetic variability in drug metabolism
    - Gene polymorphisms in hepatic enzymes that metabolize tacrolimus result in differing dosage requirements between otherwise similar individuals.
    - In the absence of genetic polymorphism testing, dosage requirements for individuals must be tailored to their specific needs.

DIAGNOSIS

1. Tacrolimus trough level monitoring
    - Trough level is a *surrogate marker* for total drug exposure, which is more completely represented by the AUC (area under the distribution curve) of timed drug levels measured in pharmacokinetic studies. Patients are targeted to a specific drug exposure that is approximated by achieving a range of C0 trough level.
    - Trough levels are monitored at most clinical encounters, including each scheduled clinic visit.
    - Trough level monitoring should be employed routinely during all acute hospitalizations, to check for trough variability associated with medication changes, food intake and acute gastrointestinal illness. This should include at minimum upon admission and as part of discharge planning for the hospitalization.
    - Trough level monitoring is used to verify attainment of target 5-7 days following most changes in drug dosing.
    - Only morning trough levels are clinically interpretable for dose titration, due to diurnal differences in tacrolimus pharmacokinetics.

2. Pharmacokinetics (PK)
    - Full PK profiling is impractical in a routine clinical setting. Tacrolimus total drug exposure can be estimated effectively with a limited sampling PK strategy, to more accurately measure the drug exposure for a given dose of medication.
    - Few studies have specifically tested outcome based on AUC, ranging from 150-210 mcg.h/L in the first 4-6 weeks, to 100-125 mcg.h/L more long term. At these levels, excess drug toxicity is usually avoided.
    - Tacrolimus PK is recommended at set intervals in the first year after transplantation, in association with mycophenolate PK studies. Initial PK studies in the first month, to test the correlation of achieved C0 trough levels with AUC and for dose adjustment accordingly. Additional PK study should be completed after the baseline level of immunosuppression is achieved, following taper.
    - Additional PK studies may be performed in the setting of uncertain drug exposure for a given dose, such as following acute rejection in the setting of apparently acceptable trough drug levels.
    - PK may also me indicated for dose-finding in the setting of suspected non-adherence and high trough level variability.

3. Quantification of trough level variability (CV)
    - The level of trough variation between doses is associated with inconsistent dose timing or non-adherence to medication.

- It can be quantified by calculating the coefficient of variation (CV), using trough drug levels over a period of time (e.g. 6, 12 months).
  CV = standard deviation (SD) of levels/mean, for a given period
- Adjustment for changing trough targets can be made to provide similar information, using the SD of the difference from trough to target for each dose.

MANAGEMENT

1. Starting dose peri-transplant for tacrolimus varies according to age, due to differences in drug metabolism.
   - Age <12: 0.2 mg/kg/dose every 12 hours
   - Age 12 and over: 0.1 mg/kg/dose every 12 hours
   - The first dose of tacrolimus is administered on admission, prior to transplant and continued q.12 h.
   - See section above on interaction with corticosteroids, in order to effectively titrate tacrolimus when it is co-administered with IV/PO steroids at the time of transplant.

2. Standard tacrolimus trough targets after transplant vary according to the organ transplant received
   - See ***organ-specific targets***, according to time after transplant Individual patient targets may differ from the standard protocol, depending on patient-specific factors.

3. Further adjustment (individualization) of tacrolimus trough level (C0) targets may be recommended based on PK test results to achieve targeted AUC.
   - At routinely scheduled PK studies, dosage and C0 target will remain unchanged if the patient is achieving the desired drug exposure (within acceptable deviation).
   - The ratio of AUC to C0 for tacrolimus is typically ~17, but may vary significantly between patients depending on their individual drug metabolism profiles. This AUC/C0 ratio may be used to personalize the C0 trough target needed to achieve the desired target AUC, especially in the setting of identified drug toxicity or suspected sub-therapeutic immunosuppressant exposure.
   - Patients with slower tacrolimus metabolism (AUC/C0 <15) may experience sub-therapeutic drug exposure (AUC) at standard targets, and may be at an increased risk for subclinical rejection. In such cases, modified C0 targets may be recommended based on the PK data to achieve the intended therapeutic drug exposure.
   - Patients with faster tacrolimus metabolism (AUC/C0 >19) calculated excess drug exposure (AUC) but with C0 achieving the target range, should be screened for potential adverse effects that may be associated with excess immunosuppression (e.g. AKI, physical symptoms, hematopoetic suppression, histological signs).
   - In the setting of fast metabolism (confirmed by PK testing) and evidence of AKI or histologic changes suggesting ischemia, consider use of medications like diltiazem, which slow tacrolimus metabolism.
   - When new chronic medications are introduced that are known to affect tacrolimus metabolism, repeat PK testing is recommended once the new steady state is achieved, to verify that individualized targets remain applicable.

4. During treatment of acute rejection
   - Target trough levels are typically increased to the next higher level, according to the standard post-transplant targets.

- See the guidelines for treatment of acute TCMR

5. Titration of drug dosing to attain the prescribed trough level
   - Drug dosage adjustment is considered if the trough level is outside of the prescribed target range.
   - No dosage adjustment is required when trough level falls within the target range.

6. Confirm the validity of testing time first, when targets fall outside the prescribed range
   - Confirm that the trough level falls within the 11-13 hour window and is reliable for clinical decision-making.
   - Early drug levels (<11 hours) are most likely to result in higher trough levels, making high levels uninterpretable. Low drug levels in this setting suggest insufficient drug exposure and should be acted upon.
   - Late drug levels (>13 hours) are most likely to result in lower trough levels, making low levels uninterpretable. High drug levels in this setting suggest excess drug exposure and should be acted upon.
   - For extended-release tacrolimus, the similar guideline applies to drug levels obtained <23 or >25 hours post dose.
   - In the setting of early/late drug levels, motivational interviewing techniques should be used with families to improve the timing of testing and preserve accurate reporting of "last dose" administered before the test.

7. Screen for risk factors that may implicate changes in drug metabolism or absorption
   - Ask about change in health status, gastrointestinal disease, food intake with medication, new medications or recent change in dose of the primary drug.
   - Screen for non-adherence: Ask for number of missed or late doses in the last 14 days.
   - Significant increase (>20% above) or decrease (>20% below) target range

8. Titrate drug dosing by protocol depending on the level
   - In the absence of identified complicating risk factors, the Transplant Nurse/Pharmacist may be delegated to titrate the medication dose according to the ***dose titration protocol*** (see below).
   - If a risk factor is identified (acute illness, high C0 variability or suspected non-adherence), medication dose changes must always be reviewed first by the transplant physician.

9. Tacrolimus dose titration protocol
   - Trough level that is taken <11 hours or >13 hours should not be considered invalid, and should not be used for dose titration. In such cases, the level should be repeated.
   - Trough levels that were previously on target and now just slightly outside of the target range (within 10% below or above target) should be checked again at the next scheduled testing to confirm that the deviation is persistent before making dose changes.
   - Trough levels that are persistently 1-10% outside of target range twice in a row or more significantly increased (11-20% above) or decreased (11-20% below) should automatically result in dose adjustment.
   - For patients who have been on a previously stable dose of medications, larger dose changes should be avoided. Usually the dose will be increased or decreased by approximately ***10-15% of the total daily dose*** to achieve the target.

- In the setting of high dose-sensitivity, the lowest dose that achieves a trough above the lower limit of the target range is used.
- ***Tacrolimus doses should not be held***, unless there is clear evidence of dose-related toxicity. Holding tacrolimus dose(s) may result in a period of insufficient drug exposure until the new drug dose achieves steady state.
- When steady-state conditions apply, a new dose of tacrolimus can be estimated by the ratio of the new target AUC and the actual measured AUC with the current dose. Since the relationship is roughly linear, the same estimation can be applied by taking the ratio of target/actual drug level and multiplying with the current *total daily dose*.

  New dose = previous dose * TAC C0 target/TAC C0 measured.

10. Dose titration of liquid vs. capsules
    - Liquid medications may be titrated to an accuracy of 0.1 mg doses and should have the same dose for the am and pm dose, every 12 hours.
    - Capsule medications are limited to 0.5 mg increments of dose. Patients are usually initially prescribed a dose that is the same for the AM and PM dose.
    - Uneven dosing is generally avoided, but may be needed at lower doses to achieve the ~10-15% change in dose to achieve target, or when larger changes result in swings above/below the target range.
    - When uneven dosing is used, the ***smaller dose is given in the PM***. (e.g. 1.5 mg at 08:00, and 1.0 mg at 20:00). This ensures that the morning trough level reflects the minimum drug exposure.

MONITORING

1. Immediately post-transplant dose-finding or during hospitalization for acute illness
    - Repeat drug levels are obtained on a daily basis to determine the trend in change of drug exposure in the acute setting.
    - Initial changes in dose should be deferred for the first 48-72 hours, unless trough level below target is identifying risk for insufficient dosage. The trough level trend over the first 2 days is used to evaluate the need for and magnitude of dose adjustment.
    - Changes in drug dose in response to these levels should be limited to not more than every 2 days, unless there is associated drug toxicity or serious risk associated with sub-therapeutic drug exposure.

2. Repeat routine monitoring (monthly)
    - For drug levels within the target range
    - For levels 1-10% outside of range for the first time (i.e. previous level in range).

3. Short-term repeat trough level monitoring in specific situations (within 5-7 days, as it takes up to 5 days to achieve a new steady state after a change in drug dosing)
    - If the timing of the trough level (early or late) makes the drug level uninterpretable.
    - After every dose adjustment.

ORGAN SPECIFIC TARGETS

Organ-specific targets for tacrolimus trough level monitoring
The target AUC is derived from available targets in the literature, and the ratio of previously targeted range (mean) and expected AUC. Achieved AUC +/- 30 from the targeted AUC would generally be considered adequate.

Heart Transplant (16.3:1, based on KT data)

Time post-transplant	Tacrolimus Target (µg/L)	$AUC_{0\text{-}12h}$ (µg*h/L)
0-6 months	10-12	179
6-12 months	8-10	147
Year 2 and 3	6-8	114
> 3 years (no rejection)	4-6	100

Kidney Transplant (16.3:1)

Time post-transplant	Tacrolimus Target (µg/L)	$AUC_{0\text{-}12h}$ (µg*h/L)
1st month	10-15	210
1-3 months	8-12	170
4-6 months	6-10	140
>6 months (no rejection)	5-8*	110

*4-7 in low-risk patients without rejection

Liver Transplant (15.1:1)

Time post-transplant	Tacrolimus Target (µg/L)	$AUC_{0\text{-}12h}$ (µg*h/L)
TBC		

The relationship between tacrolimus C0 (trough) and AUC is linear and in most studies is high. The ratio of AUC to C0 is estimated at between 15:1 and 16.3:1 (3, 4, 6-12).

RELATED DOCUMENTS

Standard operating procedure for tacrolimus dose titration by nursing staff
V:\Multi_Organ\SOPs\Tests and Procedures\Tacrolimus TDM\SOP Tacrolimus dose titration 2015-01-09.doc

Protocol for use by nursing staff for tacrolimus dose titration
V:\Multi_Organ\SOPs\Tests and Procedures\Tacrolimus TDM\TAC Dose Titration Protocol 2015-04-11.doc

Flow diagram (algorithm) to direct tacrolimus dose titration
V:\Multi_Organ\SOPs\Tests and Procedures\Tacrolimus TDM\TAC Dose Adjustment Flow Diagram.pptx

Ambulatory clinical note to document protocol-driven dose adjustments
V:\Multi_Organ\SOPs\Tests and Procedures\Tacrolimus TDM\TAC Dose Adjustment Ambulatory Note (OPD).docx

Excel spreadsheet to calculate CV of TAC trough levels over a period of time
Trough CV Calculator.xlsx

Education materials and standard orders for PK testing
V:\Multi_Organ\SOPs\Tests and Procedures\PK Testing for TAC and MMF

REFERENCES

1. Anglicheau D, Flamant M, Schlageter MH, Martinez F, Cassinat B, Beaune P, et al. Pharmacokinetic interaction between corticosteroids and tacrolimus after renal transplantation. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2003;18(11):2409-14.
2. Greanya ED, Poulin E, Partovi N, Shapiro RJ, Al-Khatib M, Ensom MH. Pharmacokinetics of tacrolimus and mycophenolate mofetil in renal transplant recipients on a corticosteroid-free regimen. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2012;69(2):134-42.
3. Kim JS, Aviles DH, Silverstein DM, Leblanc PL, Matti Vehaskari V. Effect of age, ethnicity, and glucocorticoid use on tacrolimus pharmacokinetics in pediatric renal transplant patients. Pediatr Transplant. 2005;9(2):162-9.
4. van Duijnhoven EM, Boots JM, Christiaans MH, Stolk LM, Undre NA, van Hooff JP. Increase in tacrolimus trough levels after steroid withdrawal. Transplant international : official journal of the European Society for Organ Transplantation. 2003;16(10):721-5.
5. Lam S, Partovi N, Ting LS, Ensom MH. Corticosteroid interactions with cyclosporine, tacrolimus, mycophenolate, and sirolimus: fact or fiction? The Annals of pharmacotherapy. 2008;42(7):1037-47.
6. Scholten EM, Cremers SC, Schoemaker RC, Rowshani AT, van Kan EJ, den Hartigh J, et al. AUC-guided dosing of tacrolimus prevents progressive systemic overexposure in renal transplant recipients. Kidney Int. 2005;67(6):2440-7.
7. Wallemacq P, Armstrong VW, Brunet M, Haufroid V, Holt DW, Johnston A, et al. Opportunities to optimize tacrolimus therapy in solid organ transplantation: report of the European consensus conference. Ther Drug Monit. 2009;31(2):139-52.

8. Zhao W, Fakhoury M, Baudouin V, Maisin A, Deschenes G, Jacqz-Aigrain E. Limited sampling strategy for estimating individual exposure of tacrolimus in pediatric kidney transplant patients. Ther Drug Monit. 2011;33(6):681-7.
9. Delaloye JR, Kassir N, Lapeyraque AL, Alvarez F, Lallier M, Beaunoyer M, et al. Limited sampling strategies for monitoring tacrolimus in pediatric liver transplant recipients. Ther Drug Monit. 2011;33(4):380-6.
10. Lee MN, Butani L. Improved pharmacokinetic monitoring of tacrolimus exposure after pediatric renal transplantation. Pediatr Transplant. 2007;11(4):388-93.
11. Claeys T, Van Dyck M, Van Damme-Lombaerts R. Pharmacokinetics of tacrolimus in stable paediatric renal transplant recipients. Pediatr Nephrol. 2010;25(2):335-42.
12. Schubert M, Venkataramanan R, Holt DW, Shaw LM, McGhee W, Reyes J, et al. Pharmacokinetics of sirolimus and tacrolimus in pediatric transplant patients. Am J Transplant. 2004;4(5):767-73.

DOCUMENT HISTORY

VERSION	EFFECTIVE DATE	WRITER	REASON
Draft	December 19, 2014	TBH	Initial creation of draft guideline
01	April 16, 2015	TBH	Initial approval and implementation
02	Jan 31, 2016	TBH	Updated with recommendations on steroid interaction and management of potentially toxic high drug levels.
03	TBC	TBH/KH	Updated with individualization and minor edits for clarity.