

**Use of sublingual tacrolimus in adult blood and
marrow transplant patients: a pilot study**

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Department of Pharmacy
Research Proposal

Use of sublingual tacrolimus in adult blood and marrow transplant patients: a pilot study

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Abstract

Barriers to oral (PO) tacrolimus in recipients of an allogeneic blood or marrow transplant (BMT) are not uncommon and often result in reliance on intravenous (IV) tacrolimus, a formulation which is fraught with concerns. Sublingual (SL) administration of tacrolimus is widely used as a safe and effective alternative in the solid organ transplant population. Similar benefits may be appreciated by patients undergoing BMT, including avoidance of risks and expense associated with IV tacrolimus, as well as reduced pill burden and limited trough variability relative to PO tacrolimus. This study will establish feasibility and gather preliminary data on the dose conversion ratio of PO to SL tacrolimus through comparison of trough concentrations drawn during PO and SL tacrolimus delivery during routine laboratory monitoring. Results will be used to inform future studies in larger cohorts and assist in determining an accurate conversion ratio, which is imperative to inform clinician decision-making and allow for prescription of doses which result in trough levels that ensure the safety and efficacy of tacrolimus.

Specific Aims

- 1) Demonstrate feasibility of SL administration of tacrolimus in blood and marrow transplant (BMT) patients
- 2) Gather preliminary data to determine the conversion ratio of oral (PO) to sublingual (SL) administration of tacrolimus needed to achieve equivalent whole blood concentrations in BMT patients

Background and Significance

Tacrolimus is a calcineurin inhibitor frequently used in the prevention of graft-versus-host disease (GVHD) in recipients of an allogeneic blood or marrow transplant (BMT).^(1–5) Unfortunately, barriers to oral (PO) medication administration are not uncommon in this population and include severe mucositis, dysphagia, altered mental status, intubation without oral access and high-output diarrhea. In such cases, clinicians are often forced to rely on intravenous (IV) administration of tacrolimus, a formulation which is fraught with concerns. Studies describe higher rates of nephrotoxicity and neurotoxicity with IV compared to PO tacrolimus and reports of life-threatening cardiac arrhythmias and anaphylaxis to the castor oil component exist.^(6–9) An alarmingly high rate of PO to IV dose calculation errors has been described, likely due in part to inconsistent reports of dose conversion ratios.⁽¹⁰⁾ Additionally, dilution of the concentrated IV product to the appropriate dose is challenging and administration requires extended infusion times of 12 to 24 hours to minimize fluctuations of blood levels. This can complicate administration of other medications in patients with limited IV access and also result in erroneous reporting of blood concentrations, should blood for assay be taken from the line in which tacrolimus is being infused. The IV product is also more costly than other formulations and thus increases healthcare expenses for institutions and patients alike.^(11,12) At Mayo Clinic, the institutional cost of doses <5 mg is \$330 per day, compared to \$0.98 per 1 mg oral capsule. It is for these reasons an alternative to IV tacrolimus administration is desirable.

Sublingual (SL) administration of tacrolimus is widely used as a safe and effective alternative to the IV product in the solid organ transplant (SOT) population.^(12–17) It has been adopted routinely in the heart, lung and abdominal solid organ transplant practices at Mayo Clinic in Rochester. More recently it has been used successfully in the prevention of GVHD in pediatric transplant patients.⁽¹⁸⁾ Tacrolimus can be administered sublingually by opening a capsule and placing the contents under the tongue, with patients instructed not to swallow until after dissolution occurs and avoid eating, drinking

or suctioning of secretions for the subsequent 15 to 30 minutes.(10–12,14,16,18,19) Patients were able to achieve goal trough levels using SL tacrolimus with minimal, if any, reported adverse effects. Published literature indicates the area under the blood-concentration-time curve (AUC) for SL tacrolimus is well correlated with whole blood trough levels, the current standard of care for therapeutic drug monitoring and guidance of dose adjustments to maintain concentrations within the desired therapeutic window.(11,12) In addition to serving as a safe and effective alternative to IV administration in patients who become intolerant of oral medications, the SL formulation offers advantages over PO tacrolimus as well. When administered orally, tacrolimus has poor bioavailability (approximately 25%) due to extensive first-pass metabolism and P-glycoprotein efflux.(20) These concerns are mitigated with SL administration, which allows for direct absorption into the blood. Avoidance of first-pass metabolism may also minimize the degree of interaction between tacrolimus and drugs that effect hepatic cytochrome P-450 enzymes.(18) Reduced doses with SL administration can also decrease pill burden and cost associated with tacrolimus use.(12,15,16) Studies undertaken to determine the optimal SL to PO dose conversion ratio in SOT patients report slightly variable results depending on the type of organ received,(10–12,14,16) with most centers recommending a ratio of 1:1 or 1:2.(17) Given that enteral and first-pass hepatic metabolism are bypassed with the SL route, one report suggests that a ratio of 1:1 be used when major drug interactions are present.(14)

While the volume of data surrounding SL tacrolimus is growing in SOT, published reports describing its use in BMT are extremely limited and entirely lacking in an adult BMT population. Determination of the feasibility of administration and pharmacokinetic parameters in this cohort is an essential exploratory step toward establishing SL administration as an alternative to IV tacrolimus for patients undergoing BMT who are unable to tolerate the PO formulation. The purpose of this study will be to gather preliminary data related to feasibility and dose conversion with SL administration in clinically stable adult BMT patients. Results will be used to in future studies evaluating use of SL tacrolimus in peri-transplant and hospital settings, where IV tacrolimus is used in patients intolerant of PO tacrolimus. Determining an accurate conversion ratio is imperative to inform clinician decision-making and allow for prescription of doses that result in trough levels which ensure both safety and efficacy.

Preliminary Studies

Prior studies using SL tacrolimus in the SOT population have been conducted in patients with varying degrees of illness and in numerous settings. They investigate both transient and long-term use SL tacrolimus in the inpatient and outpatient environment. These demonstrate patients are able to achieve goal trough levels using SL tacrolimus with limited adverse effects, which are confined to adverse taste. The SL formulation shows excellent bioavailability due to direct absorption into the bloodstream and an AUC that is well correlated with whole blood trough levels. To date there is a single 5-patient case series describing SL tacrolimus use to achieve safe and effective trough concentrations in pediatric BMT patients. Doses ranged from 0.025-0.078 mg/kg/day in divided doses.

Research Design and Methods

Overview

This is a prospective, single-center, crossover, pilot study of consecutive patients undergoing allogeneic blood or marrow transplantation (BMT) at Mayo Clinic in Rochester Minnesota. It will include adult (age ≥18 years) patients prescribed tacrolimus for treatment or prevention of graft-versus-host disease (GVHD) who transition between

orally administered tacrolimus and the sublingual (SL) route of administration. We will report feasibility of the SL formulation in the population and preliminary data on the SL:PO dose conversion ratio.

Setting

This study will be conducted in Rochester, Minnesota, where Mayo Clinic completes over 700 blood or marrow transplants per year, approximately 20% of which are allogeneic transplants. Around half of these will receive tacrolimus for GVHD prevention. As a referral center, patients are diverse with respect to diagnosis and demographics. Comprehensive care is provided by a multidisciplinary treatment team including physicians from a variety of medical specialties, advanced practice providers, pharmacists, nurses, dieticians, care coordinators and social workers. Integrated inpatient and outpatient care allows for close monitoring of patients throughout the care continuum, with near-daily appointments and twice weekly tacrolimus laboratory monitoring conducted locally through day +30 following transplant or longer, as dictated by a patient's medical course.

Identification of Study Subjects

Individuals will be identified from within the adult allogeneic BMT program at Mayo Clinic in Rochester, Minnesota. Participants will **include** adults prescribed tacrolimus for treatment or prevention of GVHD. Vulnerable populations, patients with contraindications to tacrolimus, inclusive of hypersensitivity, history of posterior reversible encephalopathy syndrome or calcineurin-inhibitor induced thrombotic microangiopathy, and those lacking the capacity to consent in English and declining to participate in research will be **excluded**.

Patients will be screened when scheduled for their pre-transplant pharmacist visit. Those meeting inclusion and exclusion criteria will be enrolled during a regularly scheduled pre-transplant clinic appointment. Here they will be supplied with HIPAA Authorization and consent forms. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record. Fifteen minutes, or additional time as necessary, will be allowed for discussion and patient questions. Patients will be informed their care will not be impacted by declining to participate in the study.

Definitions

Dose-adjusted conversion ratio of SL and PO tacrolimus (16):

- Calculated using the concentration-to-dose ratios for each route of administration
- $[(\text{Blood concentration}_{\text{SL}}/\text{daily dose}_{\text{SL}})/(\text{Blood concentration}_{\text{PO}}/\text{daily dose}_{\text{PO}})]$

Steady state trough: obtained following stable/unchanged dosing for a minimum of 4 dosing intervals (ie, prior to the 5th scheduled dose at the earliest)

Major drug interactions with tacrolimus, ie strong CYP3A4 inhibitors and inducers

- Inhibitors: azole antifungals, macrolide antibiotics, protease inhibitors (ex. ritonavir, boceprevir) and
- Inducers: antimycobacterials (ex. rifabutin, rifampin), anticonvulsants (phenytoin, carbamazepine and phenobarbital)

- Data including new start or dose changes made in the 7 days preceding a steady state trough level for either route of administration will be collected for purposes of a secondary analysis

Hepatic dysfunction: liver function tests (AST or ALT) >3x the upper limit of normal or any stage of cirrhosis documented as part of the patient's electronic health record (EHR).

Study Procedure

Enrolled patients will enter the study at their pre-transplant clinic appointment in the outpatient setting, with tacrolimus started at day -3 prior to transplant. Prescribers will issue a prescription for tacrolimus in the usual way and the recommended starting dose will be in accordance with the established protocol (0.04 mg/kg/dose of ideal body weight), initially administered sublingually. In accordance with current protocols and standards of care, additional dose adjustments may be made at the discretion of the treating provider or consulting pharmacist based on their clinical assessments. A pharmacist or member of the investigative team will provide consultation to assist with this process. At this time the patient will also be provided with a drug diary for recording the dose (in milligrams), time, and route of administration for each dose taken.

Around allogeneic transplant, as standard of care patients are maintained on tacrolimus with therapeutic drug monitoring performed through collection of whole blood trough levels a minimum of twice weekly, or at steady state after a dose change, to ensure concentrations are within the desired therapeutic window. For the purposes of this study, enrolled patients will begin administering their existing tacrolimus capsules sublingually. Patients and caregivers will be educated to open the capsules and place the entire contents under the patient's tongue. Patients will be instructed not to swallow until absorption is complete (typically within 1-2 minutes) and avoid eating and drinking 15 minutes following administration. Doses should be given at 12-hour intervals. Patients and caregivers will be instructed to record the day, time and route of each dose in a drug diary for review by providers or pharmacists at subsequent clinic visits (Appendix A).

The dose titration and monitoring process will not deviate from usual care in this setting. Determination of goal trough level and dose changes will be at the discretion of the treating provider and not influenced by this study. Trough levels will be drawn Mondays and Thursdays, or at steady state after a dose change, as a component of routine lab monitoring. This is consistent with standard of care and usual post-transplant procedure, meaning no additional blood samples will be required for completion of this research. Should a sub- or supra-therapeutic trough be discovered in advance of this and the tacrolimus dose adjusted, 4 dosing intervals will be required on the new dose before a trough concentration will be used in study analysis. The same is true if a dose is withheld or missed in accordance with provider instructions or patient report. At each patient encounter, the provider seeing the patient will inquire about potential barriers to SL administration and record patient responses on a study data collection form (Appendix B), as well as review the patient's drug diary for any missed doses. Both the data collection form and drug diary will be scanned into the patient's EHR. Should the patient not provide their drug diary at the time of the clinic visit, a detailed history will be recorded by the provider and assessed for compliance. Only trough levels drawn during periods of full compliance will be used for study purposes. Study personnel will be available via pager to assist providers with dose adjustments based on lab results as they become available and changes will be communicated to patients in the usual

manner, either by phone or through the patient online portal. Study personnel will also be available as a resource for patients or providers during appointments if needed. Patients are instructed to contact a provider via a 24-hour phone line or through the online patient portal in the event of questions or concerns.

Cross-over to orally administered tacrolimus can occur immediately after a steady-state trough has been obtained on the initial dosage form, or as dictated by the patient's clinical status and ability to tolerate the alternative route of administration. Doses may be chosen based on provider discretion in light of drug interactions, clinical status and initial trough information. A subsequent tacrolimus trough will be obtained on PO tacrolimus in the same manner in which it was measured during the 1st phase, after which point the study period will conclude.

Data Collection

Demographics including age, gender, underlying hematologic diagnosis, type of allogeneic transplant (related, unrelated, or cord blood) and source (peripheral blood or bone marrow) will be collected from the EHR. Conditioning regimen, existing drug interactions, comprehensive GVHD prophylaxis strategy, diagnosis of hepatic dysfunction, and date of transplant will be reported. The new introduction or dose change of a medication with major interaction with tacrolimus (see "Definitions" above) within the 7 days prior to study entry or during enrolled will be noted.

Daily tacrolimus dose, reasons for withholding (if applicable), and patient-reported barriers to SL administration will be recorded. Trough levels for each route of administration will be collected after at least 4 consecutive doses for determination of the SL to PO conversion ratio.

Outcomes and Analysis

The primary endpoint is documentation of feasibility of SL tacrolimus administration in BMT patients. The secondary endpoint will be to determine the conversion ratio of SL:PO administration of tacrolimus, normalized for dose. Descriptive statistics will be reported related to remaining data including existing drug interactions and comprehensive GVHD prophylaxis strategy.

Patient report of barriers to administration of SL tacrolimus will be used to investigate feasibility of the SL formulation. These could include poor tolerability of the SL route, lack of understanding related to the administration instructions, or inability to refrain from eating or drinking for the defined amount of time. As described in "Study Procedure", these will be recorded at each clinic appointment when the patient sees a provider during the study timeframe. Per-protocol analysis will be conducted to determine the conversion ratio of SL and PO administration. Median dose conversion ratios will be compared between patients with new major drug interactions or undergoing dose changes of these medications and the remainder of the cohort.

We aim to include a total of 10 patients for analysis. This represents approximately 10% of the number needed to determine in future study the true conversion ratio with a 10% margin of error (n = 97 patients), assuming an estimated conversion ratio of 0.5 (extrapolated from available literature in the SOT population). Continuous data will be described using median (IQR). The conversion ratio of SL:PO administration of

tacrolimus will be calculated as described above for each patient (note that this is adjusted for the daily dose administered). Each subject will serve as his or her own control. The median will be determined for the cohort and by subgroup, as described in the paragraph above.

Data Storage

Data will be extracted from the EHR by select study personnel and stored in a password-protected Research Electronic Data Capture (REDCap) database. This platform meets the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliance, with password protection and the ability to assign access levels that ensure tightly regulated data sharing. All source data will be de-identified so that only a unique study number bearing no relationship to personal identifiers will be used to identify participants. Only the investigators involved in the collection and analysis of the data will have access to information with individually identifiable private information about the human subjects. Reported data will be de-identified and presented only in composite form.

Potential Risks and Benefits to Patients

Potential risks to study participants are minimal and comparable to those of PO tacrolimus. Sublingual administration specifically has been well-tolerated in numerous reports with limited to no side effects. Reports are inclusive of a wide variety of patient populations, such as adult and pediatric patients and in lung, liver, kidney and blood and marrow transplant settings. At present, no study reports a serious side effect related to SL tacrolimus use and outcomes do not suggest risks for any adverse effects are elevated when comparing SL to PO tacrolimus. Possible unique side effects include metallic or bitter taste of the medication. Serum trough levels may fluctuate within or outside of the therapeutic window when switching between SL and PO formulations, but are monitored closely. Similar fluctuations can also occur as a part of routine treatment with PO tacrolimus due to changing clinical status, interacting medications or dietary intake. Risks in the acute care setting associated with tacrolimus use via any route include peripheral edema, pruritus, constipation, diarrhea, nausea, vomiting, anemia, changes in leukocyte count, thrombocytopenia, headache, tremor, paresthesia, and increased serum creatinine. More serious yet uncommon adverse events include liver and renal toxicity, posterior reversible encephalopathy syndrome, infection, seizure, or hemolytic uremia syndrome. No additional risk for these adverse events is conferred with the use of SL tacrolimus (relative to oral) based on the available literature. Additionally, numerous data demonstrate the safe and effective use of tacrolimus in blood and marrow transplant for GVHD. It remains a cornerstone of internationally ratified guidelines as well as Mayo Clinic clinical practice. Patients will be closely monitored by a multidisciplinary medical team, who are well-educated on the risks, as part of the standard of care procedures. Other risks associated with blood and marrow transplant exist and are expected but will not be captured as a part of this research. No additional clinic visits, blood sampling, or medication will be required for completion of this study, thus no cost is associated with the transition to SL tacrolimus.

Potential benefits to study participants include reduced pill burden and decreased intra-patient variability of trough levels, due to the ability of SL administration to bypass first-pass hepatic metabolism and drug efflux from the P-glycoprotein in the intestine. Significant scientific gains may be appreciated through demonstration of feasibility for this route of medication delivery. Initial data will illuminate a PO to SL conversion ratio which can be tested in a larger cohort of outpatients and extrapolated to environments in

which IV tacrolimus is currently used, most notably the peri-transplant period and inpatient environment. Determination of this ratio will improve clinicians' ability to prescribe doses that result in trough levels that ensure safety and efficacy when transitioning patients to SL tacrolimus.

Data Safety and Monitoring

The principal investigator (PI) or designated co-investigator will ensure screening was compatible with inclusion and exclusion criteria and confirm documentation of informed consent within 24 hours of patient enrollment. The PI or designated co-investigator will be informed of concerns by providers directing patient care as they occur and review records within 24 hours of notification. The PI will be responsible for ensuring participants' safety on a daily basis. This includes assuring routine trough monitoring for safety and efficacy is performed, weekly review of new records for potential adverse events related to SL administration of tacrolimus and reporting of serious adverse events and unanticipated problems to the Institutional Review Board (IRB).

References:

1. Sabry W, Le Blanc R, Labbé A-C, Sauvageau G, Couban S, Kiss T, et al. Graft-versus-Host Disease Prophylaxis with Tacrolimus and Mycophenolate Mofetil in HLA-Matched Nonmyeloablative Transplant Recipients Is Associated with Very Low Incidence of GVHD and Nonrelapse Mortality. *Biol Blood Marrow Transplant*. 2009 Aug;15(8):919–29.
2. Cutler C, Logan B, Nakamura R, Johnston L, Choi S, Porter D, et al. Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. *Blood*. 2014 Aug 21;124(8):1372–7.
3. Ho VT, Aldridge J, Kim HT, Cutler C, Koreth J, Armand P, et al. Comparison of Tacrolimus and Sirolimus (Tac/Sir) versus Tacrolimus, Sirolimus, and Mini-Methotrexate (Tac/Sir/MTX) as Acute Graft-versus-Host Disease Prophylaxis after Reduced-Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2009 Jul;15(7):844–50.
4. Chhabra S, Liu Y, Hemmer MT, Costa L, Pidala JA, Couriel DR, et al. Comparative Analysis of Calcineurin Inhibitor–Based Methotrexate and Mycophenolate Mofetil–Containing Regimens for Prevention of Graft-versus-Host Disease after Reduced-Intensity Conditioning Allogeneic Transplantation. *Biol Blood Marrow Transplant*. 2018 Aug 25;20(6):837–43.
5. Martin PJ, Rizzo JD, Wingard JR, Ballen K, Curtin PT, Cutler C, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2012 Aug;18(8):1150–63.
6. Hirano Y, Sugimoto S, Mano T, Kurosaki T, Miyoshi K, Otani S, et al. Prolonged administration of twice-daily bolus intravenous tacrolimus in the early phase after lung transplantation. *Ann Transplant*. 2017;22:484–92.
7. Takamatsu Y, Ishizu M, Ichinose I, Ogata K, Onoue M, Kumagawa M, et al. Intravenous cyclosporine and tacrolimus caused anaphylaxis but oral cyclosporine capsules were tolerated in an allogeneic bone marrow transplant recipient. *Bone Marrow Transplant*. 2001 Aug 18;28(4):421–3.
8. Hodak SP, Moubarak JB, Rodriguez I, Gelfand MC, Alijani MR, Tracy CM. QT prolongation and near fatal cardiac arrhythmia after intravenous tacrolimus administration: a case report. *Transplantation*. 1998 Aug 27;66(4):535–7.
9. Johnson MC, So S, Marsh JW, Murphy AM. QT prolongation and Torsades de Pointes after administration of FK506. *Transplantation*. 1992 Apr;53(4):929–30.
10. Collin C, Boussaud V, Lefeuvre S, Amrein C, Glouzman AS, Havard L, et al. Sublingual tacrolimus as an alternative to intravenous route in patients with thoracic transplant: A retrospective study. *Transplant Proc*. 2010;42(10):4331–7.
11. Solari S, Cancino A, Wolff R, Norero B, Vargas JI, Barrera F, et al. Sublingual tacrolimus administration provides similar drug exposure to per-oral route employing lower doses in liver transplantation: a pilot study. *Aliment Pharmacol Ther*. 2017;45(9):1225–31.
12. Federico S, Carrano R, Sabbatini M, Nappi R, Russo L, Apicella L, et al. Sublingual administration improves systemic exposure of tacrolimus in kidney transplant recipients: comparison with oral administration. *Eur J Clin Invest*. 2016;46(7):651–7.
13. Pennington CA, Park JM. Sublingual tacrolimus as an alternative to oral administration for solid organ transplant recipients. *Am J Heal Pharm*. 2015;72(4):277–84.
14. Tsapepas D, Pharm D, Saal S, Benkert S, Levine D, Ph D, et al. Sublingual Tacrolimus : A Pharmacokinetic Evaluation Pilot Study. 2013;33(1):31–7.

15. Hanger KM, Boettger RF, Watkins KD, Leard LE, Golden JA, Hoopes CW, et al. A Pharmacokinetic Analysis of Oral vs Sublingual Administration of Tacrolimus in Lung Transplant Recipients. *Chest*. 2010;138(4):542A.
16. Watkins KD, Boettger RF, Hanger KM, Leard LE, Golden JA, Hoopes CW, et al. Use of sublingual tacrolimus in lung transplant recipients. *J Hear Lung Transplant*. 2012;31(2):127–32.
17. Doligalski CT, Liu EC, Sammons CM, Silverman A, Logan AT. Sublingual administration of tacrolimus: Current trends and available evidence. *Pharmacotherapy*. 2014;34(11):1209–19.
18. Amelon E, Rumelhart S, Cleppe J, Modi A. Sublingual Administration of Tacrolimus for Graft-Versus-Host Disease Prevention in Pediatric Allogeneic Hematopoietic Stem Cell Transplantation, a Case Series. *Biol Blood Marrow Transplant*. 2018;24(3):S336.
19. Nasiri-Toosi Z, Dashti-Khavidaki S, Nasiri-Toosi M, Khalili H, Jafarian A, Irajian H, et al. Clinical pharmacokinetics of oral versus sublingual administration of tacrolimus in adult liver transplant recipients. *Exp Clin Transplant*. 2012;10(6):586–91.
20. Venkataramanan R, Swaminathan A, Prasad T, Jain A, Zuckerman S, Warty V, et al. Clinical pharmacokinetics of tacrolimus. *Clin Pharmacokinet*. 1995 Dec;29(6):404–30.

Appendix B

Feasibility Data Collection Form

Transcript for provider questions to patient:

1. Have you experienced any difficulties taking your tacrolimus “under the tongue”?
 - a. If yes, what has been the barrier (ex. poor taste, inability to eat or drink, slow dissolution of the drug, did not understand the directions)?
2. Have you missed any tacrolimus doses since your last conversation with a care provider?
 - a. If yes, when? Why were those doses missed?
3. What concerns or questions do you have about continuing to take your tacrolimus “under the tongue”?