Current controversies on generic substitution in the transplant community

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Abstract

For drugs with a narrow therapeutic index (NTI) like tacrolimus, small changes in dosage can lead to significant changes in blood levels, which can affect both the effectiveness of the drug and the risk of adverse effects. Monitoring is crucial to ensure that the drug is maintained within the desired therapeutic range. Too low levels could lead to organ rejection, while too high levels could lead to toxicity, which can damage the kidneys, liver, and other organs.

When it comes to medications with a NTI, like tacrolimus, the issue of generic substitution becomes more complex. Due to the NTI, small variations in drug concentration can lead to significant differences in clinical outcomes. Generic drugs must be proven to be bioequivalent to the brand-name drug, which means they should have similar bioavailability (rate and extent of drug absorption) when administered under the same conditions.

It's important for individuals taking tacrolimus to communicate closely with their pharmacists, adhere to their prescribed dosage, attend all recommended follow-up appointments, and report any unusual symptoms or side effects promptly.

Keywords: tacrolimus, narrow therapeutic index, generic drugs

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Introduction

The transplant community is currently divided on whether substituting generic immunosuppressants is appropriate for recipients of organ transplants. In order to mitigate the risk of graft rejection and loss following organ transplantation, recipients of transplants require access to immunosuppressive medications (ISMs). The costs associated with ISMs can present a significant burden for transplant patients, potentially restricting access and leading to non-adherence.[1,2] The utilisation of therapeutically equivalent generic alternatives has the potential to alleviate the financial strain on both the public healthcare sector and the private sector, which is supported by medical aid in South Africa. A retrospective study conducted in the USA addressed this issue, utilising data from the Scientific Registry of Transplant Recipients spanning from 1987 to 2013.[3] The primary aim was to assess the financial implications of generic substitution of transplant medications compared to the innovator medicine. This investigation included tacrolimus, administered in kidney, liver, and heart transplant cases. The study revealed substantial cost savings with regards to tacrolimus treatment, ranging from 48% to 67% in overall per-patient expenditures. Additionally, transplant recipients managed to save between 63% and 79% of their out-of-pocket expenses.[3] Despite ongoing debates within the transplant community, uncertainties persist regarding the substitution of generic products for brand-name ISMs, as well as the interchangeability of different generic formulations.[4] Tacrolimus is a medication that belongs to a class of drugs known as calcineurin inhibitors. It is commonly used in the field of organ transplantation to prevent the rejection of transplanted organs. Tacrolimus works by suppressing the immune system's response, which helps prevent the body from attacking and rejecting the transplanted organ. However, due to its mechanism of action and the potential for serious side-effects, tacrolimus is known to have a narrow therapeutic index (NTI).[5] This review aims to define characteristics of narrow therapeutic index medicines and elucidate the stricter regulatory requirements of the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for the registration of generic medicines regarded as NTI medicines. In addition, alignment of the South African Regulatory Authority with these guidelines will also be discussed.

Narrow therapeutic index medicines and their characteristics

Defining NTI

There is no clear consensus on the definition for NTI medicines. Regulatory authorities have different definitions based on the characteristics for these medicines. The FDA defines it in terms of medicines with a narrow therapeutic ratio, where there *"is a less than a 2-fold difference in the median lethal dose (LD50) and the median effective dose (ED50) values, or a less than 2-fold difference in the minimum toxic concentrations (MTC) and the minimum effective concentrations (MEC) in the blood".* This demonstrates the importance of individualised dose titration and therapeutic drug monitoring (TDM) to ensure patient safety and efficacy of medicines. The Canadian Health Protection Bureau provides a more clinically practical definition as: *"a less than 2-fold difference in the ratio between the lowest concentration at which the clinical toxicity commonly occurs to the median concentration providing a therapeutic effect."*[6] From a clinical pharmacology perspective this is simply illustrated by the dose response curve. For NTI

medicines there is a narrow range between the concentration that is therapeutically effective and the concentration that leads to adverse events and toxicity or, on the other hand, therapeutic failure.

Characteristics of NTI medicines

Lists of NTIs are difficult to find in literature, but there is a web-enabled database called "Drug Bank" that provides a list of most medicines with a NTI. These include: aminoglycosides, monoclonal antibodies, ciclosporin, carbamazepine, digoxin, flecainide, lithium, phenytoin, phenobarbital, rifampicin, theophylline and warfarin.[7] Yu et al. summarised five common characteristics of NTIs:[8] (i) NTIs exhibit low intra-individual pharmacokinetic and pharmacodynamic variability but significant inter-individual variability; (ii) Therapeutic dosages should be individualised which requires ongoing therapeutic drug monitoring; (iii) Even a minor dose adjustment could result in a substantial change in the dose response; (iv) Dosage must be titrated in small increments and requires oversight by the attending physician; (v) Serious therapeutic failure could result from sub-therapeutic dosing, which is detrimental to transplant patients as it can lead to organ transplant rejection.[9] In addition, generic alternatives of NTIs must meet stricter bioequivalence criteria than other multisource medicines.

Bioequivalence, quality standards and generic interchangeability of NTIs

A generic medicine is manufactured to be the same as an already marketed brand-name medicine in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. These similarities help to demonstrate bioequivalence, which means that a generic medicine works in the same way and provides the same clinical benefit as the brand-name medicine. Due to the greater risk of therapeutic failure or adverse effects, both the FDA and the EMA have implemented stricter bioequivalence criteria for the registration of generic equivalents of NTIs.[8,10]

Regulatory requirements for bioequivalence in NTIs

At the 2011 FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology meeting, the regulations on establishing bioequivalence between a NTI generic and the originator were updated to a stricter limit of 10% difference in blood concentration between the originator and the generic (this relates to a range between 90.00–111.11% (note 111.11 = 1/0.9) instead of the 20% difference allowed for other generic medicines where the range limits are between 80–125% (where 125 = 1/0.8).[2,11] These regulations followed on those implemented by EMA in 2010.[2] The proposed study design to determine bioequivalence between the generic NTI and its originator is a four-way, fully replicated, crossover study in healthy subjects to compare the mean and inter-individual variability between the formulations.[8] Typically, participants are divided into four groups, each experiencing a different order of treatments, and repeating each treatment sequence with multiple participants. This design is aimed at minimising the impact of order effects and individual variability, making the results more robust and credible. A two-by-two study design is also used where one half of the group receives the originator medicine first, followed by a washout period, and then the generic medicine and vice versa for the other group. Pharmacokinetic data is gathered for the two groups and the ratio of the geometric mean value for the experimental formulation to the mean value for the standard formulation is determined for both C_{max} and AUC. Bioequivalence is demonstrated when the mean ratio's 90% confidence interval (CI) falls within a predefined range.[12]

SAHPRA guideline and regulatory requirements for biostudies of NTI medicines

To demonstrate its commitment to align with global best practices, the South African Health Products Regulatory Authority (SAHPRA) has taken an executive decision to harmonise specific policies and procedures with those of the EMA, which, in turn, is in alignment with the International Council for Harmonisation (ICH) technical requirements for medicine registration. The latest version of the SAHPRA Quality and Bioequivalence Guideline was published on the 23rd of May 2023 (found online at https://www.sahpra.org.za/document/quality-and-bioequivalence/), and includes the stricter acceptance limit for NTI APIs of a 10% difference for AUC and C_{max}, where maximum concentration is important for the safety and efficacy. SAHPRA further recognise the WHO, the FDA and other regulatory authorities for guidance when applicable.

Tacrolimus overview and the role of the pharmacist in generic substitution

Tacrolimus pharmacology

Tacrolimus, also known as FK506, is a potent immunosuppressive agent indicated for prevention of organ transplant rejection and treating conditions like atopic eczema and inflammatory eye diseases.[13-16] It is derived from *Streptomyces tsukubensis*.[17] The mechanism of action involves binding to a protein named FK506 binding protein (FKBP), leading to the inhibition of calcineurin's phosphatase activity. This enzyme, calcineurin, normally dephosphorylates the nuclear factor of activated T cells (NF-AT), a transcription factor responsible for promoting the production of IL2 and other inflammatory cytokines. By obstructing calcineurin's function, tacrolimus hinders the transcription of IL2 and other T lymphocyte cytokines.[18] Tacrolimus further enhance the actions of glucocorticoids and progesterone by binding to FKBPs inside the hormone receptor complex.[19] Since its introduction into the market in 1994 tacrolimus has been the cornerstone of immunosuppression after solid organ transplant for the prophylaxis of organ rejection. In South Africa it is indicated as primary immunosuppression in liver and kidney transplant patients and as a "rescue: therapy for heart allograft rejection.[20]

Table I: Bioequivalence studies for tacrolimus

Comparator		*n*	Patient population	Outcome	Ref.
2012 Sandoz	Randomised crossover PK of generic vs. reference	71	Intent to treat kidney transplant patients (60% Caucasian males)	Similar PK profile in kidney transplant patients	21
2011 Sandoz	Single-centre, retrospective, nonrandomised study	103	Liver or kidney transplant patients switched from originator to generic	Trough concentrations declined by average 1.98 ng/mL in liver and 0.87 ng/mL in kidney. No rejection.	22
2014 Sandoz	Prospective evaluation of systematically switching transplant recipients to generic tacrolimus	67	Kidney transplant patients (62% Caucasian males)	Generic tacrolimus statistically bioequivalent to the reference but individual patient monitoring essential	23
2010 Sandoz	Prospective, observational trial conducted at four transplant centers	70	kidney (*n* = 37), liver (*n* = 28), or multiorgan (*n* = 5) transplant patients included African American population	Tacrolimus dose requirement and trough concentrations were similar with branded and generic. Note: three times as many patients underwent dose changes after conversion to the generic	24
2013 Teva	Single-centre, prospective, randomised, cross-over, open label, steady-state bioequivalence study	35	Elderly kidney transplant patients at steady state using the originator medicine	Significantly higher systemic tacrolimus exposure with generic in elderly patients	26
2013 Sandoz	Single-centre comparison of the clinical outcomes at six months	99	Renal transplant recipients	Comparable clinical outcomes at six months in patients receiving either originator or generic from the time of renal transplantation	27
2014 Sandoz and Dr Reddy	Prospective, replicate dosing, partially blinded, randomised, 3-treatment, 6-period crossover bioequivalence study	71	Kidney (*n* = 35) or liver transplant (*n* = 36) patients	Bioequivalence (average and scaled average) criteria met between originator and two generics and between generics in kidney or liver transplant patients	25

Tacrolimus bioequivalence studies

Generic substitution in South Africa is well established to curb healthcare costs and increase accessibility to life-saving medicine. But, economic drivers should never overshadow the welfare of patients. Tacrolimus is classified as a NTI medicine and is therefore subjected to undergo *in vivo* bioequivalence studies in accordance with the FDA and EMA guidelines using the stricter criteria of a 90% confidence interval. In August 2009, the US FDA approved the first generic formulation of tacrolimus and since then a number of bioequivalence studies within the transplant patient population have been conducted (Table I). Most studies concluded that the generic tacrolimus can be safely substituted for the originator tacrolimus, and one study also found bioequivalence between two generics of tacrolimus.[21-25] These findings were however gathered in controlled clinical settings and the importance of therapeutic medicine monitoring was highlighted in all the studies and especially in elderly patients where bioequivalence could not be established.[26]

Bioequivalence studies are usually conducted in first-world countries, and not much is known about African population groups. A ten-year, single-centre longitudinal cohort study of kidney recipients, conducted between 2005 and 2015, found that the intra-patient variability in the African-American population puts them at a high risk of acute rejection.[28] Therefore, it is reassuring to know that SAHPRA has adopted the stricter bioequivalence regulations of EMA. Furthermore, the SAHPRA-approved tacrolimus prolonged-release formulations contain a bolded warning stating that these generics are not interchangeable with the immediate-release formulations of tacrolimus, unless careful monitoring and supervision by a transplant specialist (PI) is available.

Tacrolimus adverse events[29,30]

Dermatological reactions might include conditions like acne vulgaris, alopecia, pruritis, and rash. In terms of endocrine and metabolical impacts, there could be changes in serum bicarbonate and iron levels, and even the development of new-onset diabetes mellitus after transplantation (NODAT). The medication might also lead to various metabolical imbalances such as hypercalcaemia, hyperkalaemia, hyperlipidaemia, and more. Gastrointestinal adverse events include symptoms like abdominal pain, nausea, vomiting, and diarrhoea. The genitourinary system might be affected by an increased risk of urinary tract infections. Hepatic function tests could show abnormal results due to the medication. Tacrolimus might augment susceptibility to infections, including bacterial infections and viruses like the BK virus, cytomegalovirus, and others. Neuromuscular and skeletal effects might be felt as arthralgia and muscle cramps. In the realm of vision, there could be blurred vision and other visual disturbances. Ears might experience otalgia, otitis media, and tinnitus due to tacrolimus. Renal effects could include acute renal failure, increased blood urea nitrogen (BUN), elevated serum creatinine (SCr), and other kidney-related issues. Overall, tacrolimus has a wide range of potential effects on various systems in the body.

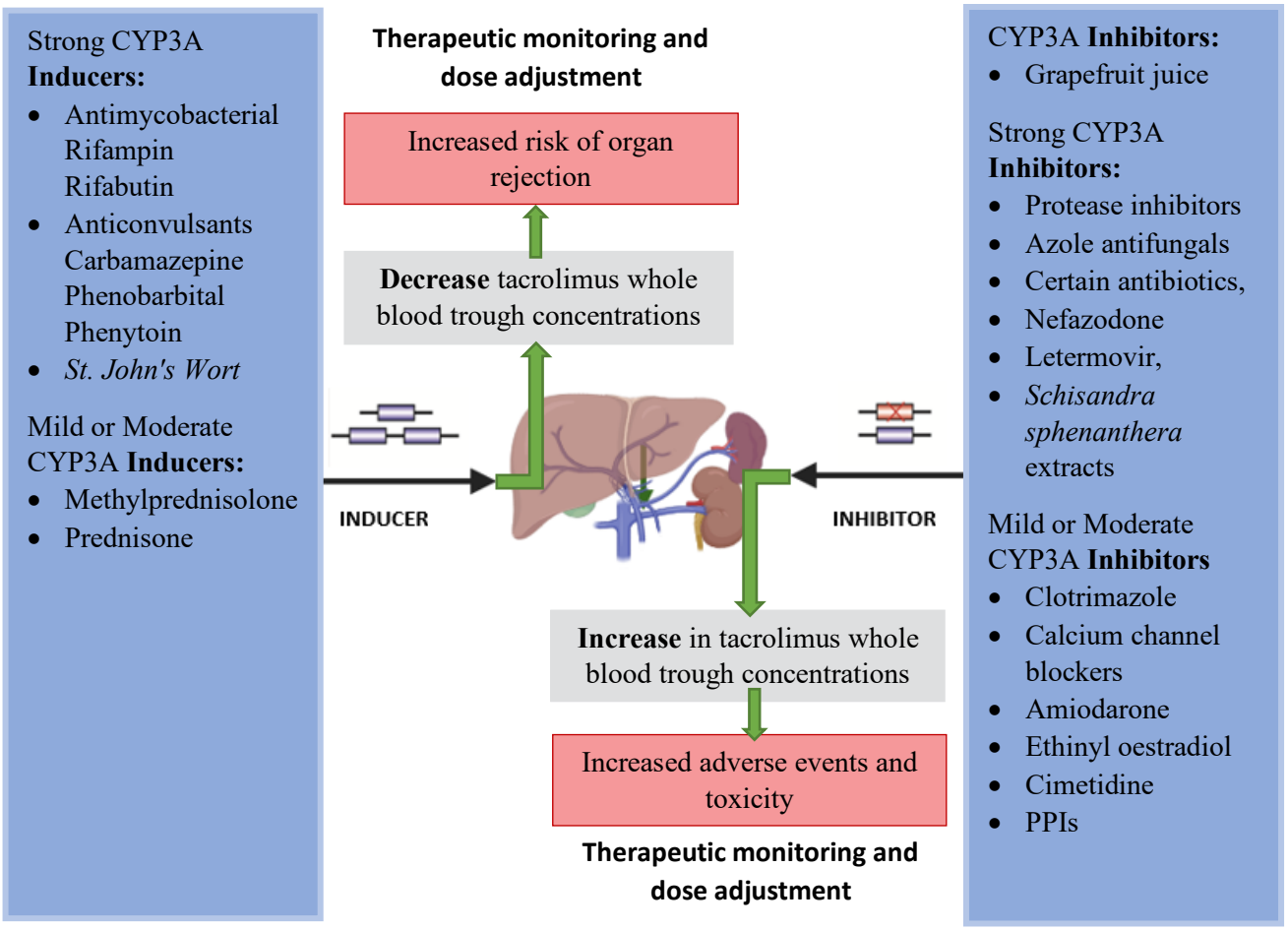

Figure 1: The influence of CYP3A inhibitors and inducers on the tacrolimus treated liver or kidney transplant patient

Drug interactions with tacrolimus[31]

Clinical and laboratory parameters should be carefully monitored during therapy with tacrolimus to prevent potential pharmacokinetic and pharmacodynamic medicine interactions. Concomitant administration of tacrolimus with inhibitors or inducers of both the Cytochrome P450 (CYP)3A metabolising enzymes and enteric multi-drug efflux transporter, P-glycoprotein, affect the blood concentration of tacrolimus.[32] Knowledge of these frequent medicine interactions is important, as they could result in therapeutic failure and acute organ rejection or toxicity due to over-exposure of tacrolimus (Figure 1). Some of the most frequent medicine interactions are given in Table II.

The pharmacist and dispensing NTIs

To reduce the potential for error, tacrolimus should be prescribed with a full description of the drug and the brand. If the brand, strength and dose frequency are not clearly stated on the prescription, the dispensing pharmacist should check with the prescriber to ensure the appropriate medicine is dispensed. A prospective, replicate dosing, partially blinded, randomised, 3-treatment, 6-period crossover bioequivalence study found that tacrolimus and two tested generic products were bioequivalent in individuals with a kidney or liver transplant.[25] The authors concluded that bioequivalence data in transplant patients were similar to that in healthy patients. Moreover, the two generic medicines evaluated in the trial were bioequivalent to each other with the tighter FDA SCABE criteria met, and there seemed to be no difference between the different tacrolimus products in terms of within-subject variability.[25] Regardless of this, studies in the genetically variable South African cohort is lacking and switching between different brands of tacrolimus requires careful therapeutic monitoring under the supervision of a transplant specialist.

The pharmacist and tacrolimus

Pharmacists play a critical role in ensuring the safe and effective use of medications with a NTI like tacrolimus. Their expertise in medication management, dosing, drug interactions, and patient education is invaluable in helping patients achieve optimal outcomes while minimising the risk of adverse effects.

Key ways in which pharmacists are involved in managing medications with a NTI like tacrolimus:

- *Dispensing and counselling:* Pharmacists ensure that patients receive the correct medication, dosage, and instructions for use. For medications with a NTI, they might provide additional counselling to patients about the importance of adhering to the prescribed dosing regimen and attending regular follow-up appointments for monitoring.

Table II: Frequent medicine-to-food and medicine-to-medicine interactions

Pharmacokinetic interactions			
PK parameter	**Interacting medicine or food**	**Effect on tacrolimus blood concentration**	**Therapeutic effect and dosage recommendations**
CYP3A Inhibitor	Grapefruit or Grapefruit Juice	Increase in tacrolimus whole blood trough concentrations.	Elevated risk of severe adverse reactions such as neurotoxicity and QT prolongation. Avoid grapefruit.
Strong CYP3A Inducers	Antimycobacterial (e.g. rifampin, rifabutin), anticonvulsants (e.g. phenytoin, carbamazepine, and phenobarbital), and St. John's Wort	Decrease tacrolimus whole blood trough concentrations, thereby increasing the risk of organ rejection.	In response, it is recommended to increase the dose of tacrolimus and regularly monitor tacrolimus whole blood trough concentrations.
Strong CYP3A Inhibitors:	Protease inhibitors (e.g. nelfinavir, telaprevir, boceprevir, ritonavir), azole antifungals (e.g. voriconazole, posaconazole, itraconazole, ketoconazole), certain antibiotics, nefazodone, letermovir, and Schisandra sphenanthera extracts	Raise tacrolimus whole blood trough concentrations. This heightens the risk of serious adverse reactions, including neurotoxicity and QT prolongation.	In cases where these inhibitors are used, it is recommended to reduce the dose of tacrolimus, with specific adjustments for voriconazole and posaconazole. Close monitoring of tacrolimus levels, starting within a few days and continuing as needed, is crucial.
Mild or Moderate CYP3A Inhibitors	Clotrimazole, certain antibiotics (e.g. erythromycin, fluconazole), calcium channel blockers, amiodarone, danazol, ethinyl oestradiol, cimetidine, lansoprazole, and omeprazole	Elevate tacrolimus whole blood trough concentrations, increasing the risk of severe adverse reactions.	To address this, regular monitoring of tacrolimus levels is recommended, along with potential dose adjustment for tacrolimus.
Other Drugs:	Magnesium and aluminium hydroxide antacids, as well as metoclopramide	Potential to increase tacrolimus whole blood trough concentrations and consequently heighten the risk of severe adverse reactions.	Regular monitoring of tacrolimus levels and possible dose adjustment of tacrolimus may be necessary.
Mild or Moderate CYP3A Inducers:	Substances like methylprednisolone and prednisone	Lower tacrolimus concentrations.	To manage this interaction, continuous monitoring of tacrolimus whole blood trough concentrations is advised, with possible adjustments to the dose of tacrolimus if required.
Pharmacodynamic medicine interactions			
Other nephrotoxic medicines	Nonsteroidal anti-inflammatory drugs, antibiotics and chemotherapeutic agents as well as ACE inhibitors	Increased nephrotoxicity with co-administration of tacrolimus.	
Tacrolimus can also aggravate the neurotoxicity of medicines such as ganciclovir.			

- *Dosage adjustment and monitoring:* Pharmacists work closely with healthcare providers to monitor patients' medication therapy. They might be involved in adjusting the dosage of tacrolimus based on the patient's response, laboratory test results, and potential drug interactions. Regular monitoring of blood levels of tacrolimus is crucial to ensure that it remains within the therapeutic range.
- *Medication reviews:* Pharmacists can conduct comprehensive reviews of a patient's medication profile to identify potential interactions or contraindications that could impact the use of tacrolimus. They can collaborate with healthcare providers to make necessary adjustments.
- *Patient education:* Pharmacists provide patients with information about the importance of taking tacrolimus consistently and as directed. They can explain potential side-effects, interactions with other medications, and the significance of regular blood tests to monitor drug levels.
- *Medication management plans:* In collaboration with healthcare providers, pharmacists can help develop medication management plans tailored to the patient's needs. This might include strategies for managing other health conditions or medications that could interact with tacrolimus.
- *Communication:* Pharmacists facilitate communication between patients and healthcare providers. They can address patients' questions, relay concerns to the medical team, and ensure that everyone involved in the patient's care is on the same page.
- *Generic substitution considerations:* If there are concerns about switching between brand-name and generic versions of tacrolimus, pharmacists can provide information about the regulatory standards for generic drugs and how they apply to NTI medications.
- *Adverse event reporting:* If a patient experiences adverse effects related to tacrolimus, pharmacists can assist in reporting these events to the appropriate channels to ensure patient safety and contribute to monitoring drug safety on a broader scale.

Conclusion

Therapeutic medicine monitoring is essential to ensure optimal patient outcomes and to prevent toxicity and possible organ rejection. This is especially important in vulnerable patient groups

including patients on polypharmacy at high risk of medicine interactions, or patients with hepatic and renal failure. The pharmacist should be able to inform patients about the possible adverse effects and medicine or food related interactions.

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