Generic Medicinal Products in Immunosuppressive Therapy—Should It be a Challenge for Therapeutic Drug Monitoring?

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Abstract: Immunosuppressants have a narrow therapeutic index (NTIDs). Indisputably cyclosporine, tacrolimus, everolimus, and sirolimus have NTIDs, and only in the case of mycophenolic acid, a scientific discussion has not been yet concluded. Their specificities highlight the implications for generics introduced into the drug market, more precisely, with bioequivalence testing. In the European Union, the European Medicines Agency (EMA) released the "*Guideline on the Investigation of Bioequivalence*." The bioequivalence (BE) of the generic (tested, T) versus original (reference, R) product should be confirmed by obtaining a 90% confidence interval (CI) for the T:R ratio of each of the 2 decisive pharmacokinetic parameters, namely, the area under the curve (AUC) between 90.00% and 111.11%. A similar approach (90.00%–112.00%) for AUC was adopted by the Canadian Agency for Drugs and Technologies in Health (CADTH) for NTIDs; however, the US Food and Drug Administration is still based on classic acceptance criteria: 90% CI between 80.00% and 125.00% but with special requirements of BE testing. A discussion about long-expected global consensus was performed in this study based on the literature concerning BE testing in the case of NTIDs. The narrow acceptance criteria reduce the potential mean difference in bioavailability between generic and original products by a few percent. To identify this problem, special attention has been paid to switching drugs (generic–generic, original–generic) and therapeutic drug monitoring after conversion (TDM). There is no global consensus on the acceptance criteria for the BE of generic drugs; therefore, consensus and harmonization are strictly necessary. This study presents a review of the generic drug market and its classification by manufacturers, drug agencies, and dates of marketing authorization. Guidelines for TDM optimization (during switching/conversion) have been proposed. Physicians and clinical pharmacists should pay special attention to switching immunosuppressive drugs between original versus generic formulations, and generic versus generic formulations. Patients and their families should be educated on the risks associated with uncontrolled conversion.

Key Words: generics, bioequivalence, immunosuppressants, TDM

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INTRODUCTION

Generics

Generics are widely used as substitutes for original drugs in immunosuppressive therapy. The safe and effective action of the original drug has been confirmed in preclinical (in vitro and in vivo) studies and clinical trials in the target patient population. For several years, the manufacturer of the original drug has benefitted from patent protection, during which other companies cannot register drugs containing the same active substance. Keeping the exclusive right to sell the original drug, the manufacturer may then earn back the costs incurred to perform clinical studies, design the drug form, and obtain marketing authorization.[1,2] At the end of this period, generic drugs may have been introduced into the pharmaceutical market by other companies. These drugs must demonstrate equivalence to the original drug, starting with the same active substance and strength. It is important that the formulation of a generic drug contain the same active substance as that of the original drug. The difference between generic and original drugs may be seen in excipients and technological aspects if this difference cannot influence the benefit-to-risk ratio of the drug. Milder marketing authorization requirements for generics and competition between vendors allow them to be much cheaper than their innovative products.[2,3] Therefore, generic drugs are attractive alternative to innovative drugs. This situation encourages national health care authorities to promote generics. It is a fact that most research, publications, and opinion articles on generics comes from developed countries (regions) where generics are registered, used, and tested. If in many developing countries the problem is limited access to (any) drug for a particular disease, then we must sadly accept that the issues of bioequivalence and therapeutic drug monitoring there are losing importance. This is the case for immunosuppressants because in the first years after organ transplantation, drug therapy accounts for 15%–25%, and in the next period, up to 90% of the total health care costs.[4,5]

According to the bioequivalence between the original drug and its generic forms, modifications may occur during pharmacotherapy. The medical doctors have the right to change the original drug to their bioequivalents—what is called "conversion."[2,5] Generic drugs are cheaper for this system, but other aspects of conversion are rarely considered. The potential costs of hospitalization, extensive therapeutic

drug monitoring (TDM) procedures, laboratory tests, and the development of TDM algorithms dedicated to these generic formulations can offset the savings from switching to a generic drug and can even favor a brand-name drug.[1,5] Despite this, in some countries such as the United States, where the market penetration of generic drugs is currently the largest, they account for more than 70% of all prescription drugs. In other countries, including many underdeveloped, the market share of such drugs is approximately 10%.[1,5,6] It seems that the market share of these drugs will increase as patents on the original medicines expire. The procedure for marketing the authorization of generics is shorter.[2,5] The sponsor must check the bioavailability relative to the original drug and prove its bioequivalence closely: pharmaceutical (in vitro) and clinical bioavailability equivalence. Clinical investigation can even be omitted when the drug release is fast, and the drug belongs to first or third class of Biopharmaceutical Classification System.[2,7,8] However, in the case of immunosuppressive agents or drugs with narrow therapeutic index, bioequivalence studies cannot be exempted.

Bioequivalence

The investigation of bioequivalence between the original drug and its generic in the standard, the simplest, form is a single-dose, 2-period, randomized, crossover, clinical study in which 18–48 healthy adult volunteers, most often men, were enrolled. Patients may be included if the investigated active substance is known to have adverse effects and the risks of its administration are unacceptable for healthy volunteers.[5,7,8] In these studies, owing to the crossover scheme, a washout phase must be considered for total drug elimination before the next period of drug administration. A bioequivalence clinical study may be planned with a parallel study; however, in contrast to the crossover scheme, a higher number of participants are required to perform a trial. It should be noted that the crossover schedule allows for the comparison of inter- and intraindividual variability, which is particularly valuable in the case of narrow therapeutic index (NTIDs). Such a scheme allows obtaining a pharmacokinetic profile after the administration of each formulation in both tested groups (randomized by formulation order, A then B, or B then A) to compare their relative bioavailability.[5]

In 2010, the FDA (US Food and Drug Administration) proposed a new approach for testing bioequivalence without a washout period after drug administration. In this case, the 4-way crossover, fully replicated design with 2 administrations of generic and reference products (also in the case of NTID's). In addition, a comparison of within-subject variances (test and reference products) is necessary to confirm that differences are not observed.[7–9]

Drugs used in investigations of bioequivalence should generally be administered under fasting conditions. In exceptional cases, for example, owing to the pharmacological properties of the drug, it may be administered with food. In bioequivalence studies, several items should be selected each time: the biological material in which the drug will be analyzed, the time and frequency of sampling, and an adequate analytical method to determine the concentration of the drug or metabolites. The applied analytical procedure must be validated and comply with the relevant acceptance criteria for unambiguous determination results. In addition, sample identification should be blinded to the analytical laboratory for adequate credibility.[2,3,5.]

Pharmacokinetic analysis is based on the determination of the following parameters: area under the curve (AUC), maximum concentration (C_{max}), and time of maximum concentration (t_{max}). In addition, other pharmacokinetic parameters are sometimes also determined, such as the elimination rate constant (k_{el}), biological half-life ($t_{1/2}$), mean residence time (MRT), and C_0 (trough-concentration), in the case of repeated dosing.

It is worth noting that considering the current guidelines, only AUC and C_{max} are decisive parameters for proving bioequivalence. It might seem that because the AUC parameter reflects the amount of drug absorbed, it is the most important factor in bioequivalence, but it is not entirely true. Of interest, C_{max} had a much greater influence on the success or failure of bioequivalence. It has been proven that C_{max} generally shows higher (even several times) interindividual variability than the AUC parameter: bioequivalence is not achieved, and it is often because of C_{max}.[5,10] During standard crossover bioequivalence studies, 2 pharmacokinetic profiles were obtained for each participant: one after administration of the comparator (original drug) and the other after administration of the potential generic. Sometimes, when the study concerned substances classified as so-called highly variable medicinal products (HVDP) presenting great (>30% CV) intraindividual variability in pharmacokinetic parameters, the study periods were doubled, and 4 pharmacokinetic profiles for one study subject were collected. Such an operation is acceptable and allows us to opt out of a large group of participating volunteers for statistical reasons.[5,10,11]In addition, it is worth noting to the fact that the bioequivalence investigation between original and generic formulation is conducted only in the group of healthy volunteers. Some transplant communities have been appealed that bioequivalence investigation of generic NTIDs needs alternative criteria of selecting participants for trials,namely, including transplant recipients in that testing. A special attention should be paid for differences in ethnic, age, sex, and comorbidities of recipients.[1]

The method of choice for the statistical analysis of bioequivalence is a multifactor analysis of variance on logarithmically transformed data—analysis of variance evaluating the effect of formulation but also of sequence, period, and subject within sequence. The target result of the calculations was the 90% confidence interval (90% CI) determined for the ratio (test/reference) of AUC or C_{max} parameters.[1,3,7]

According to these guidelines, concentration-related parameters must be subjected to a logarithmic transformation (as a result, the range of acceptance is asymmetrical). Medicinal products can be considered bioequivalent if both pharmacokinetic parameters (AUC and C_{max}) must independently satisfy the acceptance criteria.[2,5] The final acceptance of bioequivalence applied to each of the decision parameters tested.

Since August 2010, the registration of generic formulations in the European Union has been managed according to the "*Guideline on the Investigation of Bioequivalence*" released by the European Medicines Agency (EMA). The EMA guideline allows for the modification of the acceptance interval for 90% CI by extending it (only for C_{max}) to the range of even 69.84%–143.19% for HVDP drugs; however, at the same time, this guideline officially set up a class of NTIDs. For such a drug, the acceptance criteria should be more stringent, narrowing down to 90.00%–111.11%.[3] These more restricted criteria concern both the AUC and C_{max} (especially when C_{max} is important for the safety or efficacy of pharmacotherapy or TDM).[2–5,7,8] A similar approach (90.00%–112.00%) was adopted by the Canadian Agency for Drugs and Technologies in Health (CADTH) for the AUC of NTIDs,[11] whereas the FDA still applies classic acceptance criteria: 90% CI between 80.00% and 125.00%.[8,10] Global harmonization is still expected.[12,13]

Immunosuppressive Agents—the Essence of Clinical Transplantology

As mentioned above, the 5 primary drugs used in immunosuppressive therapy after organ transplantation are cyclosporine, tacrolimus (TAC), mycophenolic acid (used as mycophenolate mofetil or sodium mycophenolate), everolimus (EVE), and sirolimus (SIR). These drugs are used in therapeutic schemes, often in combinations with 2–3 immunosuppressants of the above, because they may have different molecular targets, allowing optimal therapy. In addition, it was observed that the combination of these drugs in the therapeutic schemes allows the reduction of their doses and, consequently, possible, often severe, adverse effects.

The oldest of these drugs, cyclosporine (CSA), with the trade name *Sandimmune* was introduced to the market in 1983 by *Novartis*, and its first generic equivalent was registered at the end of 1999. Cyclosporine undergoes numerous pharmacokinetic interactions, which is an additional reason for TDM. Adverse interactions are observed in combination with CYP3A4 inhibitors, such as calcium channel blockers, antifungals, and protease inhibitors. CYP3A4 inducers that potentially lower CSA levels in the blood, such as anticonvulsants and antibiotics (eg, rifampicin), should not be used during cyclosporine therapy.[14,15] The pharmacokinetics of CSA are characterized by high interindividual variability in half-life and elimination parameters; for example, more than 3 times longer $t_{1/2}$ have been observed in patients with liver diseases than in healthy volunteers.[15,16]

The other one, TAC, was introduced in 1997 under the name *Prograf* by *Fujisawa Pharmaceutical's* (currently *Astellas*) and its first generic was appeared on the market in 2009. In addition, other formulations containing TAC are used in transplantation but are not generic for *Prograf.* Unlike *Advagraf*, which is intended to be used once a day as a sustained-release preparation, *Prograf* is usually used in 2 doses per day. *Envarsus*, developed by *Chiesi*, is a hybrid sustained-release formulation.[17] Regarding pharmacokinetics, TAC is characterized by low total clearance.[18] It is absorbed from the gastrointestinal tract, and the average bioavailability of TAC after oral administration is approximately 20%–25%. In patients following a high-fat diet, reduced bioavailability has been observed, and it is recommended to use formulations containing TAC on an empty stomach for greater bioavailability.[19,20] A large volume of distribution (1300 L) was observed in healthy volunteers, indicating that the drug accumulates extensively in the body. The drug is excreted almost exclusively in feces and to a very small extent in urine.[18–20] CYP3A5 genotyping is important in predicting the initial dose of TAC in immunosuppressive therapy; after solid organ transplantation, patients who are CYP3A5 intermediate or extensive metabolizers should receive an approximately 1.5–2.0 times higher initial TAC dosage.[21]

Another widely used drug in immunosuppressive therapy, mycophenolic acid (MPA), is used as a prodrug, mycophenolate mofetil (MMF), or sodium salt of MPA (EC-MPS). Chemically, MMF is a morpholine ester of MPA that is hydrolyzed to a pharmacologically active free acid in the body. The original drug containing MMF, *CellCept* was introduced in 1995 by *Roche*, and 12 years later, the first generic drug was approved for treatment. In addition, the drug market uses a formulation containing mycophenolate sodium (EC-MPS). *Myfortic* from *Novartis*, an enteric-coated, delayed-release tablet, is intended to reduce gastrotoxic effects.[22] Administration of MPA as a prodrug (MMF) improves its absolute bioavailability by up to 94% because free MPA is absorbed very slowly from the gastrointestinal tract. In the case of EC-MPS, which is used as a delayed-release enteric-coated tablet, MPA is released only in the small intestine at a pH $>$6.0 and is assumed to be completely absorbed. The time required to achieve MPA C_{max} for EC-MPS was more than twice that required for MMF administration. However, the C_{max} of MPA was similar at equimolar doses. There was significantly higher variability in C_{max} after EC-MPS administration between patients, which was related to the nature of the enteric-coated formulation.[23,24] In addition, as shown by previous studies, it is recommended to take EC-MPS 1–2 hours after a meal because a high-fat diet can lower the C_{max} by over 30% and delay t_{max} by more than 5 hours. In these cases, the delay in the hepatic and intestinal circulation contributed to the significant differentiation of the C_{min} value. It should be noted that monitoring this parameter in therapy seems disputable; the coefficient correlation C_{min}/AUC for MMF is r = 0.48, whereas for EC-MPS, it yields only r = 0.02. MMF and EC-MPS provided comparable MPA distribution, metabolism, and excretion. They both exhibit a high oral bioavailability of approximately 80%–90%.[25]

SIR is a macrocyclic lactone that was first introduced for therapy under *Rapamune* in 1999 as an oral emulsion and 1 year later as tablets by *Wyeth* (currently part of the *Pfizer* company). After oral SIR administration, it is rapidly absorbed in healthy volunteers by approximately 1 hour, whereas in patients with kidney transplant at steady state, it is absorbed after multiple dosing at 2 hours.[26,27] It is assumed that the availability of this drug is approximately 15%, and it was noted that high-fat meals reduced C_{max} by approximately 34%. SIR is bound to albumin in 40% and is transported by the acidic P-glycoprotein (PgP). It is metabolized by cytochrome P450 and CYP3A4.[26–28] To date, 8 SIR metabolites

have been found to have weak immunosuppressive activity; however, it has been noted that the parent drug accounts for more than 90% of pharmacodynamic activity.[28]

EVE, marketed by *Novartis* under the *Afinitor/Votubia/Certican*, is more hydrophilic than SIR. Thus, EVE has a short half-life. EVE is a derivative of SIR with a similar structure but other pharmacokinetic and pharmacodynamic properties. This drug is absorbed rather quickly, that is, C_{max} yielding 1.3–1.8 hours after oral administration. A linear correlation was also observed between C_{max} and the administered dose. In contrast to SIR, a loading dose is unnecessary and may be administered once per day. In the case of EVE, a loading dose is not necessary because a steady state is not reached for 6–7 days.[29,30] EVE should be administered twice daily, as well as SIR.[28]

Immunosuppressive Agents—An Example of Narrow Therapeutic Index Drugs

Drugs defined as having an NTID are characterized not only by a narrow therapeutic concentration range but also by a steep concentration–response relationship for efficacy and/or toxicity. Their optimal use requires dose titration based on clinical effects, biochemical markers, and careful drug concentration monitoring (TDM). Primary immunosuppressive drugs (ISDs) belong to the NTID class. This is refers to the scope of cyclosporine, TAC, EVE, and SIR, and only in the case of mycophenolic acid (MPA) is debated.[1,25]

The classic acceptance range of bioequivalence (80.00%–125.00%) means approval of an average of 20% difference between the concentration-related pharmacokinetic parameters after the use of a generic versus the original drug. For this standard approach, the mean difference in percentage between generic and original products may be as high as a dozen or so, but the maximal difference between 2 different generics may even reach 28%, creating serious problems for efficient and safe pharmacotherapy with NTIDs.[5]

For immunosuppressants, the above range of values at the 90% confidence interval is controversial. It is worth mentioning that narrowing the acceptance range for the 90% CI allows reducing the permissible difference between the original and generic drug from 20% to 10%.[5,9]

Narrow acceptance ranges significantly reduced the potential mean difference in bioavailability between generic and original products by a few percent. It cannot be mathematically greater than 8%, and between the 2 generics, it will not exceed 15.5%. In an ideal world, the exposure difference between a generic and an innovative drug should not exceed 5%, and between 2 generics of the same drug, it should probably not exceed 10%.[5]

Unfortunately, generic formulations approved according to formerly accepted but more liberal rules (90% CI in the range: 80.00%–125.00%) are still available on the market.[6]

There is no global consensus on the acceptance criteria for the bioequivalence of generic drugs probably because of different health policies[4,5,8–10](Table 1). Consequently, some registration agencies, such as TGA (Therapeutic Goods Administration of Australia), recognize the generics of the bioequivalence of NTID's based on a wider range. Generics, including immunosuppressive drugs that have been authorized under older guidelines, have not been withdrawn from the drug market, and bioequivalence studies of these drugs have not referred to actual guidelines.

TDM

Monitoring the blood concentrations of immunosuppressive drugs has been a basic tool in the management of patients after organ transplantation for several decades. Perfect confirmation of this importance can be found during the introduction of the newest classic immunosuppressive drug, EVE, when the availability of a laboratory to determine EVE blood concentration was determined to be a necessary condition for administering this drug to patients after transplantation. In these patients, the primary immunosuppressive drugs are generally lifelong. Oral administration is the predominant route of administration, and immunosuppressants are most often administered twice daily.[12]

Steady-state pharmacokinetics are the easiest in practice, described by a minimum concentration (C_{min}) or by a concentration measured at another preselected time after drug administration, for example, 2 hours (C_2). Measurement of the pharmacokinetic profile expressed by the area under the curve (AUC parameter) is much more reliable. As the determination of the AUC covering the dosing interval is

TABLE 1. Pharmacokinetics Acceptance Criteria for Bioequivalence of NTID's

Drug Agency	AUC	C_{max}	T_{max}
FDA (USA) *Food and Drug Administration*	Relative average of log (AUC) (generic relative to original drug) should be in 80.00%–125.00% interval (CI = 90%)	Relative average of log (C_{max}) (generic relative to original drug) should be in 80.00%–125.00% interval (CI = 90%)	Irrelevant for bioequivalence testing
EMA (European Union) *European Medicines Agency*	Relative average of AUC (generic relative to original drug) should be in 90.00%–111.11% interval (CI = 90%)	Relative average of C_{max} (generic relative to original drug) should be in 90.00%–111.11% interval (CI = 90%)	Irrelevant for bioequivalence testing
TGA (Australia) *Therapeutic Goods Administration*	Relative average of AUC (generic relative to original drug) should be in 80.00%–125.00% interval (CI = 90%)	Relative average of C_{max} (generic relative to original drug) should be in 80.00%–125.00% interval (CI = 90%)	Irrelevant for bioequivalence testing
CADTH (Canada) *Canadian Agency for Drugs and Technologies in Health*	Relative average of AUC (generic relative to original drug) should be in 90.00%–112.00% interval (CI = 90%)	Relative average of C_{max} (generic relative to original drug) should be in 80.00%–125.00% interval (CI = 90%)	Irrelevant for bioequivalence testing

cumbersome and expensive, it is replaced in many centers by either the estimation of the AUC using the limited sampling strategy (LSS) method or by monitoring the so-called abbreviated AUC, for example, at 2 or 3 hours.5,2[1,25]

There were differences between the specific drugs in the selection of the optimal exposure marker for monitoring. Routine dosage of TAC is guided by the steady-state minimal concentration (C_{min}) because it is correlated with the AUC. However, AUC monitoring using the LSS has been used in many centers, mostly academics. In some cases, CYP3A5 genotyping is an additional indicator of TAC dose.[21] For CSA, C_{min} weakly correlated with the overall exposure (AUC); therefore, in some centers, especially in kidney transplantation, the monitored parameter was the concentration 2 hours after drug administration (C_2) as a replacement of or in addition to C_{min}. Thus, monitoring the AUC (including the LSS technique) is widespread.[5,21,28] Despite attempts to adopt C_2 concentration, monitored therapy for EVE relies on the routine determination of C_{min},28 a similar status exists for SIR. A more complex situation is with MPA, which can be administered chronically as 2 different drugs: MMF or mycophenolate sodium (EC-MPS). Plasma concentration monitoring is not an absolute requirement; however, it is recommended to achieve the target MPA concentrations for several indications in solid organ transplantation. Determination of the steady-state trough level is still widely used, although it has been proven to be a limited predictor of drug exposure. However, the $AUC_{0-\infty}$ parameter (predominantly $AUC_{0-12\ h}$), considered meaningful for its correlation with clinical effects, suffers from all the drawbacks of repeated drug concentration determinations. Hence, leading world centers have used and promoted the LSS strategy and calculation of $AUC_{0-12\ h}$ based on algorithms obtained for the therapeutic regimen used in the center or on Bayesian estimation in multicenter clinical trial populations. LSS is better documented and is more effective for MMF than for EC-MPS, and it is the recommended method for TDM.[21,25,28]

GENERIC MEDICINAL PRODUCTS OF IMMUNOSUPPRESSIVE DRUGS

To identify the problem of uncontrolled interchangeability between generic and original drugs and between different generics of the same original drug, a systematic analysis of the results of published bioequivalence studies on pharmacokinetic parameters was performed. Herranz et al[31] reported that some generic drugs of TAC (equivalent to the same original product) may have different brand names but are the same medicinal product. Therefore, they are completely interchangeable, allowing them to be treated as different batches of the same product in different packaging.[31] In our case, this application was extended to include other immunosuppressive drugs for which generics have already been introduced (CSA and MMF).

As mentioned previously, the reference range for bioequivalence of NTID's was reduced to 90.00%–111.11% (90% CI) by the EMA decision in 2010. However, it should be noted that there are generic products in this pharmaceutical market whose bioequivalence with the original drug was previously accepted with a range of 80.00%–125.00%.[3,5]

An important problem is that the manufacturer of a new generic drug is required to demonstrate the bioequivalence of the new product to the original product but is not required to make the report of this study public, whether it is a registration agency. Therefore, the scientific literature (and, to some extent, the marketing materials presented by the generic retailer) is the only source from which it is possible to evaluate the bioequivalence studies conducted, analyze the pharmacokinetic parameters, and draw conclusions regarding the safe conversion of generic drugs (Tables 2–5).

CSA

The first CSA generic equivalent was approved by the FDA in 1999. At present, there are more than 25 products on the American market at various doses and in various pharmaceutical forms (capsules and emulsions) from 8 different manufacturers and vendors. *Neoral* introduced by *Novartis* in 1995, is not a generic form of the originator *Sandimmune*, but a microemulsion form of the active ingredient with improved oral bioavailability (Fig. 1). As established, the EU-registered *Ciqorin* and *Equoral* are identical to the CSA of *Teva* and *Cyclaid* with *Ciclosporin* by *Apotex*.[11,32–34]

The results from 8 bioequivalence studies were found for the CSA. In fact, the cohort group did not have more than 50 participants.[35–40]

Wakeel et al[35] reported that the tested emulsion preparations (*Sigmasporin Microoral* versus *Sandimmun Neoral*) were biologically equivalent, both in the "wider" and the "narrower" acceptance range (n = 42). All pharmacokinetic parameters were determined at steady state. It could be falsely concluded that the generic and original drugs were switchable. However, observing the variability of results for C_{max}, the lower limit of the logarithmic value of this parameter, exceeds the range of 80.00%–125.00% (at 90% CI). This is particularly important because C_{max} is characterized by relatively high interindividual variability; therefore, it often determines the success or failure of bioequivalence studies.

In the study by Najiba et al,37 the bioequivalence between *Sigmasporin Microoral* and *Sandimmun Neoral* was also compared. A lower mean C_{max} value was observed for generic drugs. None of the mean values of the pharmacokinetic parameters were within the "narrow" acceptance interval. In addition, the results of a similar study by Mendes et al[36] in 2004 confirmed that these preparations are not completely equivalent. Therefore, it is necessary to determine whether the interchangeability of these preparations can be established. Perlík et al[16] examined and confirmed the bioequivalence of the original *Neoral* and generic *Equoral*. The mean values of the pharmacokinetic parameters (AUC, C_{max}, C_{min}), in addition to MRT, were within the acceptance range of 90.00%–111.11%, as recommended by EMA (n = 12). Hibberd et al[38] conducted a study using the enzyme multiplied immunoassay technique (EMIT; not recommended for proving bioequivalence) in a group of 33 stable patients after solid organ transplantation. During the study, a statistically

TABLE 2. Comparison of the Pharmacokinetics Parameters for MPA—Original Drug Versus Generic Drug

	Original Drug				Generic Drug			
Study Name	**AUC [mcg × h × mL^{-1}]**	**C_{max} [mcg × mL^{-1}]**	**t_{max} [h]**	**Other Parameters**	**AUC [mcg × h × mL^{-1}]**	**C_{max} [mcg × mL^{-1}]**	**t_{max} [h]**	**Other Parameters**
Masri et al.[53]		*Cellcept* [n = ND]				*MM Cept Ivax* [n = ND]		
	AUC_{0-t}	18.91 (ND)	0.63 (ND)	ND	AUC_{0-t}	19.83 (ND)	0.57 (ND)	ND
	24.35 (ND)				23.68 (ND)			
Masri et al.[52]		*Cellcept* [n = 24]				*MMF500* [n = 24]		
	AUC_{0-t}	11.68 (ND)	0.77 (ND)	ND	AUC_{0-t}	11.20 (ND)	0.71 (ND)	ND
	11.06 (ND)				11.65 (ND)			
Videla et al.[49]		*Cellcept* [n = 13]				*Linfonex* [n = 13]		
	AUC_{0-6} of:	$C_{6\ GMPA}$	ND	$C_{0\ GMPA}$	AUC_{0-6} of:	$C_{6\ GMPA}$	ND	$C_{0\ GMPA}$
	GMPA	7.16 ± 4.00		5.65 ± 2.53	GMPA	5.05 ± 2.34		3.43 ± 1.00
	52.68 ± 17.5	$C_{6\ Free\ MPA}$		$C_{0\ Free\ MPA}$	56.59 ± 43.1	$C_{6\ Free\ MPA}$		$C_{0\ Free\ MPA}$
	Free MPA	4.64 ± 4.87		3.36 ± 1.41	Free MPA	3.80 ± 2.69		3.84 ± 0.62
	22.69 ± 13.7			$C_{2\ GMPA}$	24.81 ± 6.67			$C_{2\ GMPA}$
				10.9 ± 4.00				4.08 ± 1.29
				$C_{2\ Free\ MPA}$				$C_{2\ Free\ MPA}$
				3.34 ± 1.33				4.47 ± 0.65
Estevez-Carrizo et al.[47]		*Cellcept* [n = 24]				*Suprimun* [n = 24]		
	AUC_{0-36}	10.76 (5.07)	0.67 (0.33–2.00)	k_e [h^{-1}]	AUC_{0-36}	11.86 (6.56)	0.67 (0.33–1.50)	k_e [h^{-1}]
	20.86 (6.61)			0.043 (0.019)	21.14 (7.37)			0.051 (0.027)
	$AUC_{0-\infty}$			C_{max}/AUC	$AUC_{0-\infty}$			C_{max}/AUC
	24.18 (7.33)			0.51 (0.18)	24.92 (10.33)			0.54 (0.17)
Almeida et al.[54]		*Cellcept* [n = 103]				*Linfonex* [n = 103]		
	AUC_{0-t}	1st 29.20 (26.23)	ND	$t_{1/2}$ [h]	AUC_{0-t}	1st 28.59 (31.84)	ND	$t_{1/2}$ [h]
	1st 22.26 (15.53)	2nd 30.37 (31.04)		1st 1.98 (1.35)	1st 21.46 (16.36)	2nd 31.51 (38.47)		1st 2.29 (1.73)
	2nd 23.95 (16.74)			2nd 2.24 (1.57)	2nd 24.06 (18.25)			2nd 2.58 (1.93)
	$AUC_{0-\infty}$			k_e [h^{-1}]	$AUC_{0-\infty}$			k_e [h^{-1}]
	1st 23.76 (17.57)			1st 0.53 (0.34)	1st 23.76 (17.12)			1st 0.49 (0.36)
	2nd 26.91 (21.56)			2nd 0.46 (0.32)	2nd 24.62 (15.47)			
Zhang et al.[51]		*Cellcept* [n = 18]				*Linfonex* [n = 18]		
	AUC_{0-48}	26.47 (3.67)	0.81 (0.18)	$t_{1/2}$ [h]	AUC_{0-48}	25.58 (4.79)	0.68 (0.21)	$t_{1/2}$ [h]
	58.32 (9.28)			16.04 (4.22)	59.19 (9.23)			15.12 (3.17)
	$AUC_{0-\infty}$				$AUC_{0-\infty}$			
	62.41 (10.28)				63.28 (10.23)			
Saavedra et al.[50]		*Cellcept* [n = 22]				*Linfonex* [n = 22]		
	AUC_{0-12}	33.10 (9.56)	1.70 (0.37)	ND	AUC_{0-12}	30.93 (8.46)	2.11 (0.26)	ND
	145.90 (21.67)				147.36 (32.27)			
	$AUC_{0-\infty}$				$AUC_{0-\infty}$			
	217.22 (75.35)				226.77 (109.57)			
Almeida et al.[54]		*Cellcept* [n = 116]				*IntasMMF* [n = 116]		
	AUC_{0-t}	17.59 (75.51)	0.50 (0.25–14.00)	$t_{1/2}$ [h]	AUC_{0-t}	18.03 (76.63)	0.50 (0.25–3.00)	$t_{1/2}$ [h]
	28.703 (68.14)			10.42 (5.74)	28.86 (69.49)			9.98 (4.01)
	$AUC_{0-\infty}$			k_e [h^{-1}]	$AUC_{0-\infty}$			k_e [h^{-1}]
	30.60 (69.74)			0.08 (0.03)	30.59 (69.20)			0.08 (0.03)
Sunder-Plassmann et al.[48]		*Cellcept* [n = 38]				*Myfenax* [n = 38]		
	AUC_{0-6}	16.58 ± 10.18 (3.49–48.90)	1.12 ± 0.75 (0.00–3.78)	C_{min} [mcg × mL^{-1}]	AUC_{0-6}	14.38 ± 8.50 (3.72–36.35)	1.28 ± 0.89 (0.45–3.95)	C_{min} [mcg × mL^{-1}]
	33.75 ± 15.26 (10.20–67.34)			1.57 ± 0.80 (0.34 ± 3.65)	30.77 ± 15.70 (11.21–84.95)			1.56 ± 0.72 (0.47 ± 3.18)
	$AUC_{0-\infty}$			C_0 [mcg × mL^{-1}]	$AUC_{0-\infty}$			C_0 [mcg × mL^{-1}]
	50.07 ± 21.06 (13.44–93.46)			2.72 ± 1.75 (0.50 ± 7.26)	47.31 ± 21.29 (15.68–111.9)			2.84 ± 1.86 (0.60 ± 8.72)
Danguilan et al.[55]		*Cellcept* [n = 38]				*Mycept* [n = 16]		
	AUC_{0-30}	7.88 (ND)	1.07 (ND)	ND	AUC_{0-30}	6.92 (ND)	1.03 (ND)	ND
	38.21 (ND)				36.78 (ND)			
Gonazalez-Ramirez et al.[56]		*Cellcept* [n = 10]				*TevaCept* [n = 10]		
	6.80 (1.68; 40.17)	7.10 (1.42; 16.27)	1.00 (0.5; 1.0)	ND	6.80 (1.68; 40.17)	14.15 (5.40; 18.54)	1.00 (0.5; 10.0)	ND
	median	median	median		median	median	median	
	25th; 75th	25th; 75th	25th; 75th		25th; 75th	25th; 75th	25th; 75th	

TABLE 2. (*Continued*) Comparison of the Pharmacokinetics Parameters for MPA—Original Drug Versus Generic Drug

Study Name	Original Drug				Generic Drug			
	AUC [mcg × h × mL^{-1}]	C_{max} [mcg × mL^{-1}]	t_{max} [h]	Other Parameters	AUC [mcg × h × mL^{-1}]	C_{max} [mcg × mL^{-1}]	t_{max} [h]	Other Parameters
Hong et al.[59]		*Cellcept* [n = 36]				*My-rept* [n = 36]		
	$AUC_{0-\infty}$	30.23 (10.21)	0.69 (0.47)	$t_{1/2}$ [h]	$AUC_{0-\infty}$	30.40 (13.84)	0.68 (0.28)	$t_{1/2}$ [h]
	74.09 (19.81)			17.22 (9.16)	76.48 (21.71)			19.01 (15.84)
Larpparisuth et al.[60]		*Cellcept* [n = 20]				*Immucept* [n = 20]		
	AUC_{0-12}	18.53 ± 10.93 (P = 0.22)	1.00 (0.5–2.0) (P = 0.79)	C_{min}	AUC_{0-12}	20.96 ± 10.28 (P = 0.22)	1.00 (0.5–4.0) (P = 0.79)	C_{min}
	42.19 ± 15.20 (P = 0.06)			1.00 ± 0.60 (P = 0.68)	48.27 ± 20.31 (P = 0.06)			1.04 ± 0.74 (P = 0.68)
				C_0				C_0
				2.14 ± 1.24 (P = 0.64)				2.00 ± 1.58 (P = 0.64)
Reigner et al.[58]		*Cellcept* [n = 32]				*Renodapt* [n = 31]		
	$AUC_{0-\infty}$	6.35 (58%)	0.67 (0.33–4.00)	$t_{1/2}$ [h]	$AUC_{0-\infty}$	5.70 (41%)	0.67 (0.33–3.60)	$t_{1/2}$ [h]
	26.33 (30%)			15.30 (31%)	24.97 (27%)			16.18 (50%)
Reigner et al.[58]		*Cellcept* [n = 32]				*Mycept* [n = 32]		
	$AUC_{0-\infty}$	6.35 (58%)	0.67 (0.33–4.00)	$t_{1/2}$ [h]	$AUC_{0-\infty}$	5.13 (79%)	1.17 (0.33–4.50)	$t_{1/2}$ [h]
	26.33 (30%)			15.30 (31%)	28.38 (35%)			18.18 (57%)
Reigner et al.[58]		*Cellcept* [n = 32]				*Cellmune* [n = 32]		
	$AUC_{0-\infty}$	6.35 (58%)	0.67 (0.33–4.00)	$t_{1/2}$ [h]	$AUC_{0-\infty}$	6.65 (71%)	1.33 (0.33–4.00)	$t_{1/2}$ [h]
	26.33 (30%)			15.30 (31%)	25.50 (27%)			14.98 (40%)

*For all the pharmacokinetic parameters, values are provided as means (with SD or min/max range or median or %CV) and 90% CI for C_{max} and AUC.
C_0, concentration at zero time/trough concentration; C_{max}, maximum concentration; C_{min}, minimum concentration; k_e, elimination rate constant; ND, no data; $t_{1/2}$, biological half-life; t_{max}, time of maximum concentration.

significant difference was observed between the C_{max} parameters determined after dosing with both drugs (generic *Cysporin* and the original *Neoral*). It was clearly stated that there was less absorption (C_{max}) and a slower absorption rate (t_{max}) after administration of the generic drug compared with the original drug.[38]

The generic formulation *Hexal,* for which only the AUC and C_{max} pharmacokinetic parameters were determined, delayed absorption, and consequently significantly lower C_{max} were observed as compared with *Neoral.* The calculated mean values of bioequivalence parameters ranged from 80.00% to 125.00%, which questions their responsible use in clinical practice, at least according to the EMA, CADTH, and TGA guidelines.[36] In the studies conducted by Roza et al,[39] the equivalence of *Gengraf* with the original *Neoral* was determined using a wider acceptance range. However, the mean values of pharmacokinetic parameters were also within the narrower acceptance range, both at steady state and 24 hours after administration. The exception was C_{max} for which the lower bound of the range was outside the range of 90.00%–111.11%. It is worth mentioning that *SangCyA*, the first generic CSA preparation administered as oral emulsion formulation, was withdrawn from the market because it was not bioequivalent to the original *Neoral* when taken with apple juice.[41]

TAC

Because TAC lost its patent protection in 2008, approximately 15 generic drugs have been introduced, most of which have been registered with the FDA[32–34] (Fig. 2). In addition, according to Orange Book, there is a total of 42 generic products present on the market in the United States. This is because they are registered at different strengths in the presence of dermatological forms of TAC. One of them, *Tacrolimus Watson Lab* (earlier *Actavis*), was withdrawn from the pharmaceutical market by the FDA.[34] The situation is different in Canada, where there are 5 TAC generics but a higher number of products on the market (such as the FDA, where different doses are registered for a single generic). In the EU, the first generics of *Prograf* approved by the EMA were *Cidimus* and *Crilomus*, which were identified as identical to the *Sandoz* generic. In addition, the generic *Panolimus* is available, as is the recently introduced generic from *Teva*, which is identical to *Arrow's Tacrograph*. It should also be noted that other drugs containing TAC, *Advagraf*, or *Envarsus* are not generic but original drugs with modified dosage and release compared with *Prograf.*[32–34]

For TAC, 10 publications were also found that showed bioequivalence between the original *Prograf* and the corresponding generic drugs.[18–20,31,42–47] The most reliable and widely conducted bioequivalence investigation was the study by Alloway et al[18] in 2017. The equivalence of generics named for the study as "Hi" (*Sandoz*) and "Lo" (*Dr Reddy's*) was tested in relative to the original *Prograf.* It was unequivocally shown that the ratios of geometric means for pharmacokinetic parameters confirmed bioequivalence between generics and original *Prograf* (both for the "wider" and "narrower" range). The study was conducted

TABLE 3. Comparison of the Pharmacokinetics Parameters for CSA—Original Drug Versus Generic Drug

	Original Drug				Generic Drug			
Study Name	**AUC [mcg × h × mL^{-1}]**	**C_{max} [mcg × mL^{-1}]**	**t_{max} [h]**	**Other Parameters**	**AUC [mcg × h × mL^{-1}]**	**C_{max} [mcg × mL^{-1}]**	**t_{max} [h]**	**Other Parameters**
Roza et al.[39]		*Neoral* [n = 34]				*Hexal Formulation* [n = 34]		
	AUC	*Day 1*	*Day 1*	ND	AUC	*Day 15*	*Day 15*	ND
	Day 1	1.32 (0.48)	1.60 (0.50)		*Day 15*	1.18 (0.49)	1.70 (0.60)	
	5.22 (1.73)	*Day 14*	*Day 14*		4.86 (1.76)	*Day 28*	*Day 28*	
	Day 14	1.25 (0.41)	1.50 (0.40)		*Day 28*	1.25 (0.48)	1.60 (0.50)	
	5.02 (1.65)	*Day 29*	*Day 29*		5.01 (1.77)			
	Day 29	1.27 (0.43)	1.50 (0.50)					
	5.09 (1.88)							
Kovarik et al.[30]		*Neoral* [n = 24]				*Sandimmune* [n = 24]		
	AUC	0.92 (0.22)	1.50 (1.00–2.50)	ND	AUC	0.70 (0.22)	3.30 (1.50–6.00)	ND
	3.40 (0.79)				3.89 (1.64)			
Najib et al.[37]		*Sanimmun Neoral* [n = 24]				*Sigmasporin Microoral* [n = 35]		
	$AUC_{0–72}$	0.25 (0.085)	1.44 (0.41)	$t_{1/2}$	$AUC_{0–72}$	0.23 (0.08)	1.43 (0.38)	$t_{1/2}$
	0.59 (0.25)			2.41 (1.41)	0.56 (0.30)			2.41 (1.41)
	$AUC_{0–\infty}$			k [h^{-1}]	$AUC_{0–\infty}$			k [h^{-1}]
	0.57 (0.24)			0.45 (0.36)	0.59 (0.33)			0.45 (0.36)
Talaulikar et al.[36]		*Neoral* [n = 38]				*Cysporin* [n = 24]		
	$AUC_{0–4}$	0.66 (0.07–1.17)	ND	C_0	$AUC_{0–4}$	0.74 (0.11–1.10)	ND	C_0
	1.74 (0.86–2.98)			0.11 (0.05–0.19)	2.18 (0.86–2.75)			0.10 (0.03–0.20)
	$AUC_{0–12}$				$AUC_{0–12}$			
	3.00 (1.49–5.15)				3.84 (1.31–5.09)			
Perlík et al.[16]		*Neoral* [n = 12]				*Equoral* [n = 12]		
	AUC	0.73 (0.46–1.14)	ND	C_{min} [ng/mL]	AUC	0.72 (0.94–1.15)	ND	C_{min} [ng/mL]
	3.04 (1.74–5.31)			104.00 (56.00–193.00)	3.11 (1.82–5.30)			107.00 (56.00–205.00)
				MRT [h]				MRT [h]
				8.01 (5.47–11.77)				8.40 (0.89–1.21)
Hibberd et al.[38]		*Neoral* [n = 33]				*Cysporin* [n = 33]		
	$AUC_{0–12}$	0.88 (0.37)	1.4 (0.6)	$t_{1/2}$ [h]	$AUC_{0–12}$	0.75 (0.30)	1.90 (0.8)	$t_{1/2}$ [h]
	3.85 (1.38)			8.70 (6.20)	3.49 (1.32)			8.80 (4.30)
Pollard et al. (2001)		*Neoral* [n = 34]				*Hexal Formulation* [n = 34]		
	$AUC_{0–72}$	0.98 (0.23)	ND	ND	$AUC_{0–72}$	0.86 (0.15)	ND	ND
	3.97 (0.92)				3.61 (0.66)			
	$AUC_{0–\infty}$				$AUC_{0–\infty}$			
	4.09 (0.94)				3.71 (0.69)			
Wakeel et al.[35]		*Sanimmun Neoral* [n = 42]				*Sigmasporin Neoral* [n = 42]		
	AUC_{ss}	0.97 (0.40)	1.60 (0.70)	C_{min} [ng/mL]	AUC_{ss}	0.90 (0.35)	1.50 (0.70)	C_{min} [ng/mL]
	3.78 (1.61)			117.20 (62.80)	3.63 (1.42)			115.60 (62.80)
				MRT [h]				MRT [h]
				4.10 (0.60)				4.20 (0.60)
Pamugas et al.[40]		*Neoral* [n = ND]				*Arpimune* [n = ND]		
	logAUC	1.15 (0.32)	2.00 (0.30)	ND	logAUC	1.45 (0.31)	1.87 (0.27)	ND
	3.66 (0.35)				3.66 (0.35)			

*For all the pharmacokinetic parameters, values are provided as means (with SD or min/max range or median or %CV) and 90% CI for C_{max} and AUC.

C_0, concentration at zero time/trough concentration; C_{max}, maximum concentration; C_{min}, minimum concentration; k_e, elimination rate constant; ND, no data; $t_{1/2}$, biological half-life; t_{max}, time of maximum concentration.

in 2 groups of patients: after kidney transplantation (n = 35) and after liver transplantation (n = 36). This is the first prospective, randomized, partially blinded, triple, six-period, crossover, bioequivalence study on immunosuppressive drugs. The limitations of this study result from the fact that it was performed under fasting conditions; therefore, it is not

TABLE 4. Comparison of the Pharmacokinetics Parameters for TAC—Original Drug Versus Generic Drug

	Original Drug				Generic Drug			
Study Name	**AUC [ng × h × mL^{-1}]**	**C_{max} [ng × mL^{-1}]**	**t_{max} [h]**	**Other Parameters**	**AUC2 [ng × h × mL^{-1}]**	**C_{max} [ng × mL^{-1}]**	**t_{max} [h]**	**Other Parameters**
Park et al.[44]	*Prograf* [n = 29]				*TacroBell* [n = 29]			
	AUC_{0-t} 196.80 (116.67)	17.46 (10.51)	1.5 (0.6)	C_{min} 1.71 (1.38)	AUC_{0-t} 224.34 (159.58)	23.34 (11.83)	1.5 (2.4)	C_{min} 2.14 (2.24)
	$AUC_{0-\infty}$ 217.70 (133.08)			$t_{1/2}$ [h] 26.90 (10.90)	$AUC_{0-\infty}$ 253.75 (191.82)			$t_{1/2}$ [h] 31.70 (31.70)
	AUC_{0-24} 108.91 (66.43)				AUC_{0-24} 131.04 (90.31)			
Alloway et al.[18]	*Prograf* [n = 32]				*Sandoz Test* [n = 33]			
	AUC_{0-12} 60.00 (37.80)	9.10 (5.50)	1.90 (1.30)	C_0 [ng/mL] 7.00 (2.10)	AUC_{0-12} 61.80 (40.60)	9.60 (5.50)	1.50 (1.10)	C_0 [ng/mL] 7.30 (1.80)
Alloway et al.19	*Prograf* [1st period—n = 63, 2nd period—n = 55]				*Test* [1st period—n = 55, 2nd period—n = 38]			
	1st period (10 days):	1st period (10 days):	1st period (10 days):	1st period (10 days):	1st period (10 days):	1st period (10 days):	1st period (10 days):	1st period (10 days):
	AUC_{0-12} 147.90 (43.80)	23.40 (9.10)	1.40 (0.80)	C_0 [ng/mL] 9.70 (3.00)	AUC_{0-12} 164.00 (44.40)	35.10 (14.50)	1.00 (0.50)	C_0 [ng/mL] 9.80 (2.50)
	2nd period (6 months):	2nd period (6 months): 19.60 (7.40)	2nd period (6 months): 1.54 (1.11)	2nd period (6 months):	2nd period (6 months):	2nd period (6 months): 19.60 (9.50)	2nd period (6 months): 1.31 (0.87)	2nd period (6 months):
	AUC_{0-12} 118.50 (34.20)			C_0 [ng/mL] 6.89 (2.20)	AUC_{0-12} 106.80 (34.70)			C_0 [ng/mL] 5.65 (1.60)
Taube et al.[20]	*Prograf* [n = 207]				*TAC Sandoz* [n = 207]			
	AUC_{0-t} 31.60 (16.40)	3.71 (1.39)	1.50 (0.50–3.00)	$t_{1/2}$ [h] 37.00 (11.00)	AUC_{0-t} 32.80 (16.70)	3.47 (1.35)	1.50 (0.75–4.00)	$t_{1/2}$ [h] 36.00 (10.00)
	$AUC_{0-\infty}$ 39.80 (22.60)				$AUC_{0-\infty}$ 41.00 (22.80)			
Taube et al.[20]	*Prograf* [n = 43]				*TAC Sandoz* [n = 43]			
	AUC_{0-t} 32.20 (19.60)	3.21 (1.27)	1.50 (0.75–2.67)	$t_{1/2}$ [h] 35.00 (4.00)	AUC_{0-t} 34.30 (18.60)	3.25 (1.19)	1.25 (0.75–3.50)	$t_{1/2}$ [h] 36.00 (8.00)
	$AUC_{0-\infty}$ 35.50 (20.20)				$AUC_{0-\infty}$ 37.20 (19.10)			
Jacobo-Cabral et al.[43]	*Prograf* [n = 29]				*Limustin* [n = 9]			
	AUC 125.00 (43.30)	19.80 (7.30)	ND	AUC/Dose 76.40 (44.60)	AUC 65.80 (39.05)	7.00 (3.80)	ND	AUC/Dose 40.50 (44.40)
				C_{max}/Dose 11.60 (5.70)				C_{max}/Dose 4.20 (4.30)
				C_0 [ng/mL] 6.90 (2.70)				C_0 [ng/mL] 5.10 (3.30)
Mohanty et al.[45]	*Prograf* [n = 52]				*Tacpan* [n = 52]			
	AUC_{0-72} 348.34 (156.41)	40.62 (11.30)	1.50 (0.75–3.50)	ND	AUC_{0-72} 361.04 (158.71)	46.20 (10.73)	1.38 (0.75–4.00)	ND

*For all the pharmacokinetic parameters, values are provided as means (with SD or min/max range or median or %CV) and 90% CI for C_{max} and AUC.

C_0, concentration at zero time/trough concentration; C_{max}, maximum concentration; C_{min}, minimum concentration; k_e, elimination rate constant; ND, no data; $t_{1/2}$, biological half-life; t_{max}, time of maximum concentration.

possible to deduce possible changes in pharmacokinetics resulting from irregular meals.[18] This study is an extension of the observations conducted in 2014 by the same team leader.[18,19] Interestingly, 90% CI values for the geometric mean AUC and C_{max} ratios were within a fixed range of 80.00%–125.00%, thus meeting the FDA criteria for bioequivalence. The stricter AUC criteria set by EMA (90.00%–111.11%) and CADTH (90.00%–112.00%) were satisfied. In the case of the average C_{max} values (geometric mean), we noted compliance with the FDA, CADTH, and TAG acceptance ranges; however, in the case of the EMA guidelines, they have not been met. As discussed in that study, C_{max} is not critical for monitoring the efficacy and safety of TAC.[18–20] In another study conducted by Taube et al,[20] the

TABLE 5. Comparison of the 3 TAC Generic Products and *Prograf* by Herranz et al.[31]

	Generic						Original	
	PharOS		***Sandoz***		***Intas***		***Prograf***	
PharOS			C_{max}	*Homosedastic:* 5 mg: 98.47–123.70 1 mg: 98.47–123.70 0.5 mg: 98.55–120.28	C_{max}	*Homosedastic:* 5 mg: ND 1 mg: 89.03–112.38 0.5 mg: 89.03–112.38	C_{max}	5 mg: 105.56–117.93
			AUC	*Homosedastic:* 5 mg: 84.12–105.30 1 mg: 84.12–105.30 0.5 mg: 80.16–101.04	AUC	*Homosedastic:* 5 mg: ND 1 mg: 88.74–113.35 0.5 mg: 88.74–113.35	AUC	5 mg: 93.06–104.74
Sandoz	C_{max}	*Heterosedastic* 5 mg: 98.72–123.39 1 mg: 98.72–123.39 0.5 mg: 98.55–120.28			C_{max}	*Homosedastic:* 5 mg: ND 1 mg: 79.81–102.92 0.5 mg: 81.86–103.12	C_{max}	5 mg: 91.69–111.46 1 mg: 94.26–111.42
	AUC	*Heterosedastic* 5 mg: 86.84–102.00 1 mg: 86.84–102.00 0.5 mg: 81.44–99.45			AUC	*Homosedastic:* 5 mg: ND 1 mg: 97.48–116.50 0.5 mg: 99.84–124.39	AUC	5 mg: 99.24–110.89 1 mg: 101.12–119.01
Intas	C_{max}	*Heterosedastic* 5 mg: ND 1 mg: 90.85–110.13 0.5 mg: 90.85–110.13	C_{max}	*Homosedastic:* 5 mg: ND 1 mg: 79.81–102.92 0.5 mg: 81.86–103.12			C_{max}	1 mg: 103.00–120.80
	AUC	*Heterosedastic* 5 mg: ND 1 mg: 91.37–110.08 0.5 mg: 91.37–110.08	AUC	*Homosedastic:* 5 mg: ND 1 mg: 97.48–116.50 0.5 mg: 99.84–124.39			AUC	1 mg: 91.51–105.90

C_{max}, maximal concentration; ND, no data.

bioequivalence of 3 TAC generic drugs *PharOS*, *Intas*, and *Sandoz* was demonstrated. Only the latter met the EMA acceptance criteria requirements for both C_{max} and AUC. By contrast, in this study, the C_{max} tested after single-dose administration was not clinically relevant.[20] Min et al[42] reported that bioequivalence studies in healthy volunteers administered with a single dose may not provide a sufficient guarantee of therapeutic equivalence between the original (*Prograf*) and generic (*Tacrobell*) drugs in organ transplant patients. In this study, 10 days after drug administration, the C_{max} of the generic drug was significantly higher than the C_{max} of the innovator drug. Interestingly, in the same study,

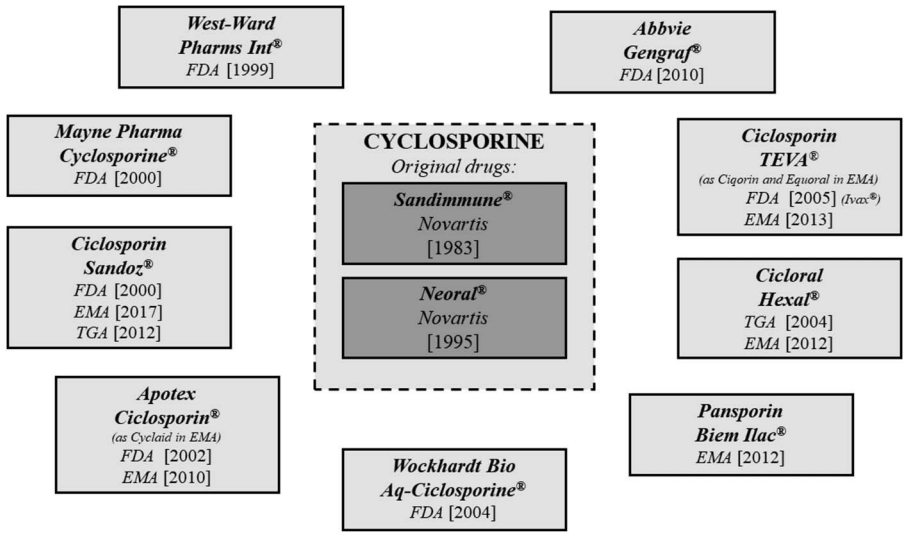

FIGURE 1. CSA generics scheme.

it was found that after 6 months of pharmacotherapy, the mean C_{max} for both formulations were eliminated, and no statistically significant differences were observed. The limitation of this study, however, is the poor racial diversity of the patients, most of whom were Asians. After analyzing the results, the authors attempted to formulate dosing recommendations for generic *Tacrobell* to maintain the appropriate "therapeutic window," C_{max} and AUC, a dose 10% lower than that of the branded product should be used, and the C_{min} should be 15% lower than that for the original product.[42] Herranz et al systematically classified the generic drugs. It was found that generic *PharOS* is, in fact, the same product as generic products from *Mylan, Stada.* In contrast, *Intas* TAC generic was identical to TAC Accord.[31] Jacobo-Cabral et al[43] paid close attention to the pediatric population. The authors pointed out that the results of bioequivalence studies in healthy volunteers could be automatically extrapolated to the pediatric population, which should not be the case. Conducting a bioequivalence study in the pediatric population may be impossible for ethical reasons. In addition, the results of this study clearly show that younger children require higher doses of drugs and, with increasing age, the bioavailability of TAC also increases.[43] Similar to previous studies, a statistically significant difference was found between the C_{max} values of the generic *Limustin* and the original *Prograf*. After 120 minutes, 100% of TAC was released from *Prograf* and only 31% from generic *Limustin*.[43] In a bioequivalence study between the generic *Tacrobell* and the original *Prograf* conducted by Park et al[44] in the Korean population, despite results significantly differing from the acceptance ranges, it was surprising that these drugs were equivalent to each other. Therefore, the published results of bioequivalence studies should be carefully interpreted. Mohanty et al[45] studied the bioequivalence testing of 2 products: the original and innovator *Tacpan* generic product was bioequivalent (90%–111%, 90% CI) to the reference *Prograf* and may be a good alternative for use in long-term immunosuppressive therapy. In this study, attention was paid to the fact that the results of bioequivalence testing should be carefully interpreted in relation to the entire population.[45] The study by Robertsen et al[46] paid a special attention for routine monitoring of TACs C_0 without describing PK profiles, especially according to the AUC parameter. In case of $AUC_{0\text{-}12}$, individual variability between original and generic formulation oscillates in range 10%–56% for more than 70% of patients in that study. For C_{max} parameter, the individual variability range has been wider, namely, 12%–131% characteristic for 85% transplant patients. The differences in determined TAC trough concentration were not statistically significant. In case of generic *Tacni*, PK profiles of elderly transplant recipients in absorption and distribution phases were significantly different—the higher systemic exposure for TAC was observed in case of generic. Conversely, similar mean values of C_0 evidence of practically the same PK profile of elimination phase. To sum up, in that case, classic routine C_0 monitoring of TAC did not allow to identify of clinical not-bioequivalence of generic *Tacni* with original *Prograf* formulation.[46]

MMF

Another immunosuppressive drug with generic forms on the market is MMF. In 2008, 3 pharmaceutical companies registered their first generics in parallel: *Sandoz, West-Ward Pharma*, and *Teva*. The first 2 companies registered their formulations with the FDA, whereas *Myfenax* was registered in the EU by the EMA (Fig. 3). It should be noted that only 2 generic drugs, MMF *Accord* and *Mylan*, were identified as identical generic formulations. It is worth mentioning that the FDA withdrew 3 generic drugs from the American pharmaceutical market, including the generic from *Apotex*, which is still authorized in Canada, the EU, and Australia.[32–34]

Eleven published studies comparing the bioequivalence of MMF generics and the innovative drug *CellCept* were evaluated.[47–56] Estevez-Carrizo et al[47] in their study drew attention to the ratio of C_{max}/AUC, which in their opinion seems to be a better indicator of the degree of absorption than C_{max}. Contrary to the C_{max} parameter itself, this ratio does not depend on the time of drug intake by patients. This study

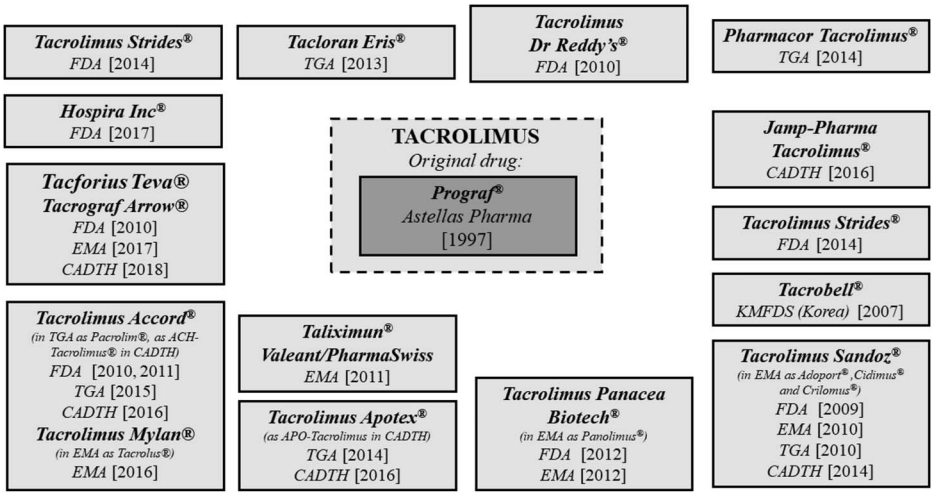

FIGURE 2. TAC generics scheme.

confirmed bioequivalence between the *Suprimun* generic and the original *CellCept*, for AUC and Cmax, with an acceptance range of 80.00%–125.00% and only for the AUC with an acceptance range of 90.00%–111.11%.[47] In the results of the Sunder-Plassmann et al,[48] C_{max} for the generic *Myfenax* was significantly lower than that for *CellCept*. However, it was demonstrated that the mean logarithmic values of these parameters at steady state were comparable in the stable transplant group. In the study by Videla et al,[49] where free MPA and GMPA concentrations were measured, 2 preparations, the generic *Linfonex* and the original *CellCept* were compared. Finally, the conversion of the original drug to a generic drug resulted in satisfactory clinical results, especially because the observation period lasted 1 year. Although this was a clinical trial of therapeutic equivalence, the pharmacokinetics data (PK) for both formulations were calculated. The Spanish population study of 2011, which examined generic *Linfonex* and original *CellCept*, at a dose of 1000 mg confirmed the bioequivalence of these preparations, both for the wider (80.00%–125.00%) and narrower (90.00%–111.11%) acceptance ranges.[49,50] A study conducted in the Chinese population,[51] in which *Linfonex* and the original *CellCept* were also compared, found a statistically significant difference between the results obtained in this study and those obtained in previous bioequivalence tests. This finding may be directly related to the fact that the populations selected for the survey had different ethnic backgrounds. Other studies concluded that the Asian population should be treated with a lower mean dose of 1.5 g per day, in contrast to the Caucasian and African American populations, which require a mean dose of 2 g/d.[25,51] Masri et al[52] conducted a bioequivalence study of the original *CellCept* and generic labeled "*MMF 500.*" The results of the study were in accordance with the acceptance range of 90.00%–111.11%; therefore, the bioequivalence of the tested drugs was confirmed. Another study by this team in 2004 showed the bioequivalence of the generic *TM-MMF* (*Ivax*) with an acceptance range of 80.00%–125.00%; however, after analysis of the presented data, it can be concluded that the logarithmic means for $AUC_{0\text{-}t}$ and C_{max} parameters are within the EMA's acceptance range.[53] A study conducted by Almeida et al[54] among healthy volunteers from the Canadian population, where the innovative *CellCept* was also compared with the generic *Limustin*, found that these drugs were bioequivalent based on European guidelines.[3,54] In an observational study performed by Danguilan et al[55] in 2014, 2 groups of kidney transplant patients were studied: one treated with the original *CellCept* and the other with the generic *Mycept*. The ratio of the mean logarithmic pharmacokinetic parameters in both groups fell within the acceptance range of 90.00%–111.11%. However, this study cannot be considered a classic bioequivalence study because it was not randomized, but it provides insight into the pharmacokinetics of MMF in transplant patients with comorbidities.[56] An interesting study was conducted in a Mexican pediatric population by González-Ramírez et al[56] The therapeutic equivalence of *Myfenax* and *CellCept* was compared in patients with end-stage renal failure awaiting transplantation. It was found that there were no statistically significant differences between the preparations regarding oral bioavailability. In addition, the release profiles were examined, and it was found that at pH equal to 1.2, drug release from the generic formulations was not statistically different from that of the original formulation. The authors expressed that data from bioequivalence studies in adults cannot be extrapolated to the pediatric population and similar data on the safety of generic forms of drugs in children.[56] In 2011, Patel et al[57] published study results comparing *Intas-MMF* generic with the original *CellCept.* This study confirmed that the 90% CI values for AUC and C_{max} complied with the European regulatory definition of bioequivalence. In addition, monitoring MPA concentrations at C_0 and C_2 for both drugs using the same approach was proposed. This study also concluded that meal intake did not significantly affect MPA absorption at doses of ≤3 g/d (in renal transplant patients). However, there was a 40% decrease in C_{max} after a meal in healthy volunteers.[3,57]

The authors of the pharmacokinetic study funded by *F. Hoffmann-La Roche* Ltd evaluating the original *CellCept* and 3 generic formulations (*Renodapt*, *Mycept*, and *Cellmune*) in

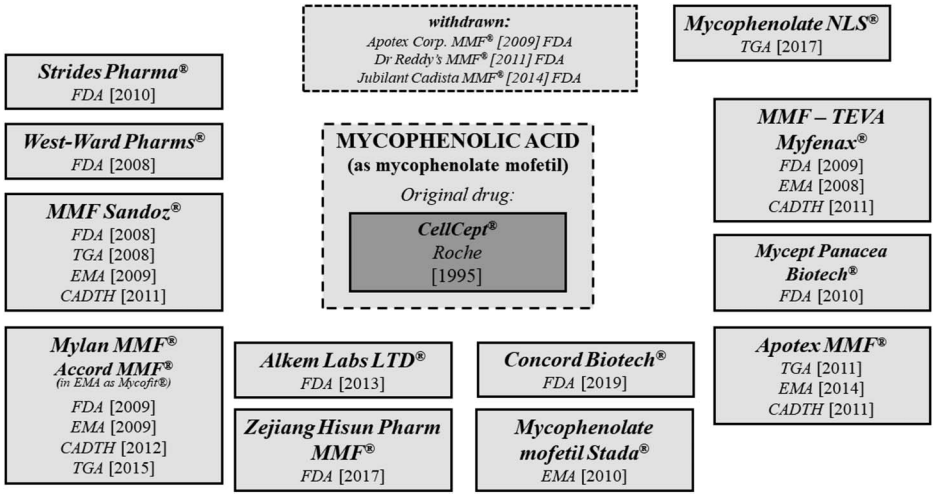

FIGURE 3. MMF generics scheme.

32 healthy volunteers observed that C_{max} intraindividual variability CV% was 48.6%, which confirms that MMF is an HVDP.[58] In such a case, the EMA guidelines suggest the application of more extended liberal criteria of acceptance for 90% CI borders.[3] Analyzing a set of individual comparisons, Reigner et al[58] found satisfactory ratios for AUCs (all 90% CI intervals within 89%–112%); unfortunately, the same was not true for C_{max} because none of the ratios for paired drugs dropped in the expected range of 80%–125%, yielding, respectively, the following values: 91%–134%, 70%–103%, 64%–94%, 73%–108%, 67%–98%, and 87%–127%. The results from this study are in good agreement with the multicenter pharmacokinetic comparison of *Myfenax* versus *CellCept* in 43 kidney transplant recipients sponsored by *Teva Europe*, a generic company.[48] The $AUC_{0\text{-}t}$ data (90% CI between 89.9% and 102.3%) complied with bioequivalence criteria; however, the ratio for C_{max} felt outside the limit (90% CI between 78.70% and 96.80%).[48] Although no study was conducted for registration purposes, their conclusions shed new light on the problematic switchability of MMF generics.

A study on generic *My-rept* and the original MMF performed in South Korea by Hong et al[59] showed a connection between the PK, clinical, and pharmacoeconomic aspects of generic MMF. *My-rept* was bioequivalent to the original MMF; however, full bioequivalence testing was not performed in this study. In that analysis, more emphasis was placed on the clinical consequences of using *My-rept* instead of *CellCept* after liver transplantation.[59] Larpparisuth et al[60] performed a pharmacokinetic comparison between the original *CellCept* and generic *Immucept* in 20 Thai patients. This study confirmed the comparable pharmacokinetic profiles of the original and generic MMF. The main limitation of this study was the use of different pharmaceutical forms of the original and generic drugs, tablets, and capsules. The PK data in this study confirmed that the Asian population required lower doses of MMF during long-term pharmacotherapy. Notably, equivalence was not confirmed because incomplete bioequivalence analysis was performed in this study.[60] The quite interesting Reigner et al[58] compared 3 generics of MMF with the original *CellCept*. *Renodapt* (Biocon Ltd., Bangalore, India), *Cellmune* (Cipla Ldt., Mumbai, India), and *Mycept* (Panacea Biotec, New Delhi, India) were selected for in vitro dissolution testing. Statistically significant differences were observed according to C_{max} parameters (according —80%–125% range), but differences in whole exposure, expressed as AUC, and t_{max} were not significant (90% CI). This study confirms that generic products could not be switched with each other—no regulations about testing generic "A'' versus generic "B'' bioequivalence.[60]

Mycophenolate Sodium (EC-MPS)

Another MPA formulation, EC-MPS, which is also used in immunosuppressive therapy, is a delayed-release, enteric-coated formulation. Although the molar equivalent doses of MMF and EC-MPS bioequivalence have been proven (only for the AUC parameter), they cannot be considered generic MMF. Therefore, products containing EC-MPS have been discussed separately.[32–34] Doses of 180 mg and 360 mg EC-MPS tablets were registered for the first time in 2005 by *Novartis* under the name *Myfortic.* For approximately 5 years, only the generic *Marelim* introduced by *Accord Healthcare*, introduced by the EMA in 2015, has been available in the European market. The same formulation was approved by the FDA in 2017; however, in the United States, there are at least 9 generic products containing MPA as a sodium salt (Fig. 4). The first generic formulation (*Apo-Mycophenolic acid,* Apotex Inc.) of EC-MPS was approved by the FDA in 2012 and Canada in 2014 by CADTH. Later, 2 generic forms were introduced in the United States by *Teva Inc.* and *RK-Pharma Inc* in 2014. In the years 2019–2021, Marcan Pharmaceuticals Inc. introduced a new generic formulation, and the FDA accepted the 5 generics of EC-MPS. Interestingly, in Australia, only the original *Myfortic* is available in the drug market, and the TGA database does not report new generic formulations containing MPS.[34]

SIR

SIR was introduced to therapy under *Rapamune* name —first in 1999 as an oral emulsion, and 1 year later as tablets —by Wyeth (now part of the Pfizer company).[32–34] Because original formulations containing SIR have been introduced for treatment relatively recently, there are few generics available in the pharmaceutical market. Currently, only the FDA and CADTH agencies have introduced a few SIR generic products. In the United States, 2 of these were introduced by *Dr Reddy's Inc* and *Zydus Pharma Inc* in 2014.[32] The situation is different in Canada, where only one generic SIR was introduced by *Rapacan-Biocon Pharmaceuticals Inc* in 2019. Recently, 5 new generics were approved by the FDA, and it seems that the number of these formulations will increase in the foreseeable future. Generic SIR products are not available in the EU and Australia, which is most likely caused by the limitations associated with patent terms. As mentioned above, there have recently been 8 available generic *Rapamune*, but there are no reports of bioequivalence studies in the literature.[32–34] Nevertheless, Bolar exemption (known in the United States as Roche-Bolar exemption) allows the bioequivalence of the original drug to be tested and to prepare its generic before the expiry of the patent period. A more generic SIR is expected to appear immediately after the end of all the protective patent terms and exclusive rights for the original *Rapamune* (Fig. 5).

EVE

EVE was introduced in 2005 by Novartis under the *Afinitor/Votubia/Certican* names in the EU, and in 2009 in the United States and Canada.[32–34] It is available in different strengths (0.25 mg—0.5 mg—0.75 mg—1 mg) as oral tablets and tablet for suspension. The first generic was preliminarily introduced by *Teva Europe*. Subsequently, in 2018, this manufacturer introduced generic EVE under the same brand name in Australia, and in 2019 in the United States and Canada. The 2 next generic forms of SIR were introduced in 2018 by *Accord* and *Sandoz/Zentiva* in the EU drug market.[32,34] The last was available in Australia and Canada in 2018 and 2020, respectively. In the past 2 years, 3 generics were initially

approved in the United States by the *Everolimus Hikma Pharms*, *Everolimus Par Pharm* in 2020, and *Everolimus BIOCON* in 2021. *Everolimus-PMS* was introduced in Canada at the beginning of 2021.[32,33]

As in the case of SIR, it is expected that a more generic EVE will appear immediately after the end of all protective patent terms for the original form (Fig. 6). A few patent terms and exclusive rights expired in the United States in 2020 (and previously in the EU), which allows new EVE generics to be introduced in the drug market.[34]

Generics of Immunosuppressive Agents—Around Conversion

According to ESOT guideline (*European Society for Organ Transplantation*) it is recommended that switching between the original immunosuppressive drug and generic formulation should be initiated only by transplant physicians.[61] Conversion initiated by a pharmacist should not occur. In addition, pharmacists should be educated about the risk of accidental conversion between generic and original products. In many countries, physicians have a right to make it clear that drug must not be changed—as a clear information for the pharmacist (eg, "non substitutable," "medical need''). Guidelines also recommended that "pharmacists should refrain from forcing generic substitution." Pharmacists should play an active role in pharmacotherapy not only to inform patients about changes in the drugs used but also to protect patients from subsequent substitutions. Unfortunately, no country has a reliable system that can inform about potential changes between brand name and generic formulations or between 2 generic drugs.[2,5,61]

Unexpected conversions can be avoided in hospitals. People in charge of hospital pharmacies should be aware that switching NTIDs drugs may be risky for patients. In such cases, the pharmacoeconomic aspect should not be considered secondary.

As the main element of posttransplant chain care, patients should be educated about any conversions between drugs and related adverse effects. They should be informed about the reasons for switching and how to identify different drug formulations. Patients should be instructed to alert their prescriber in cases of uncontrolled substitution. Variability in brand name and appearance of drug formulation may be the source of unnecessary confusion and errors for patients (eg, it may be mistaken for a dispensing error or for an additional drug in complement to the originator). The ESOT guidelines recommend monitoring drug blood concentrations for 2 weeks after substitution—additional monitoring visits and laboratory tests (eg, serum creatinine) are recommended.[61] Alloway et al[62] recommended C_0 quantification after conversion, even more so because there are no specific TDM recommendations after switching drugs. In addition, additional pharmacokinetic parameters, such as C_2, t_{max}, and terminal rate constant, are important and helpful in the comprehensive assessment of the individualization of therapy with generic drugs. Drug switching must be avoided in the early stages of transplantation. All substitutions should be initiated when the correct therapeutic window is established. In the case of generics of the same original drug, coming from the same manufacturer, switching may be recognized as safe because they are the same formulations de facto.

Every switch, including substitution from an innovative drug to a generic formulation, should be performed in a prudent manner, with careful monitoring of pharmacokinetic parameters for optimal new dose adjustment. However, switching from one ISD generic to another is risky because it is unpredictable. As reported by Al Wakeel et al,[35] immunosuppressive therapy may be initiated with generic drugs, but repetitive conversion between drugs must be avoided (perfectibility but not switchability). Two generics considered bioequivalent to an innovator may be bioequivalent between them. This problematic situation occurs when switching a generic with a slightly lower bioavailability for a generic with a slightly higher bioavailability than the originator or vice versa. Considering the worst scenario with the maximal

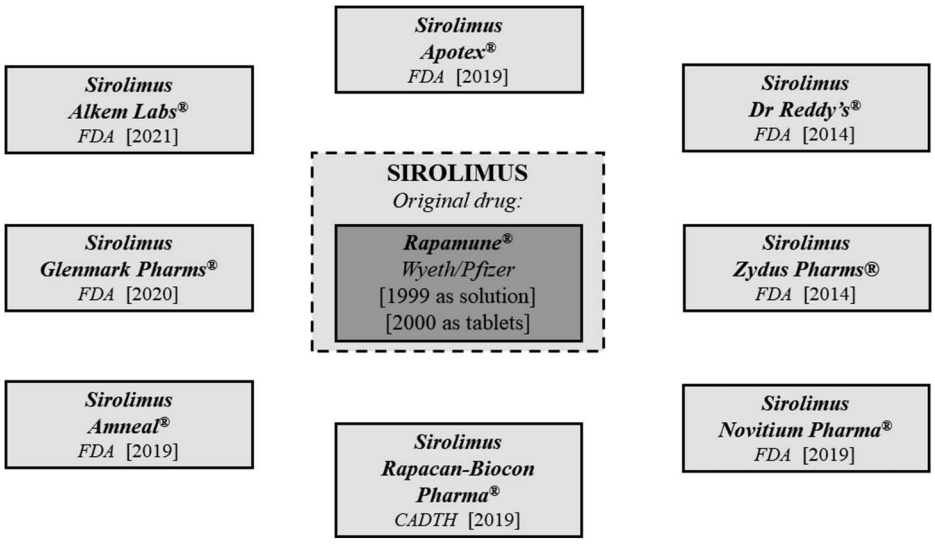

FIGURE 4. MPS generics scheme.

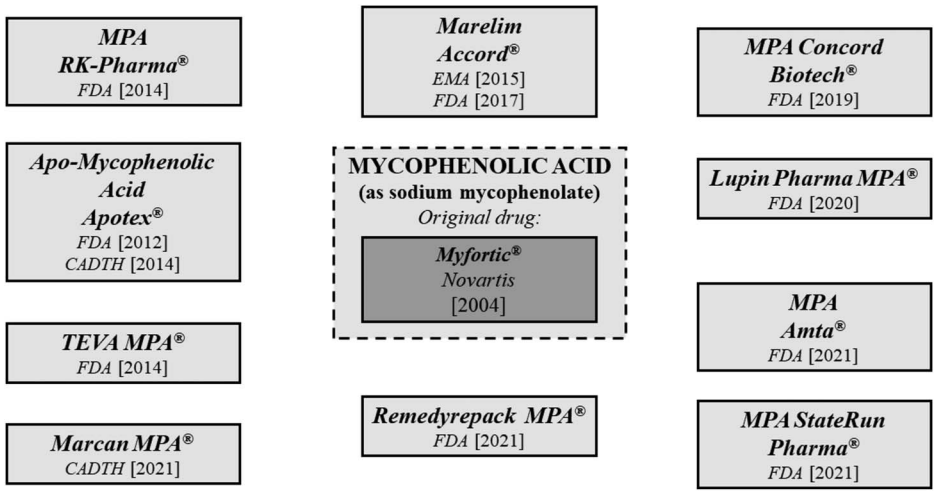

FIGURE 5. SIR generics scheme.

difference between 2 different generics, the difference may be as high as 28% when using the classic acceptance criteria (90% CI: 80.00%–125.00% or up to 15% when using 90% CI: 90.00%–111.11%). This is a reasonable argument for using narrower acceptance ranges for the ISDs. The ESOT guidelines recommend that generic formulations introduced in the market be tested for bioequivalence with other generic formulations.[59] These guidelines recommend the use of only generics in immunosuppressive therapy that meet the strict acceptance criteria. Some generics do not fulfil these criteria, but for legal reasons, changes in drug registrations cannot be enforced.

Therefore, whenever we want to switch from one generic to another, we should weigh up many arguments in favor and against.

Generics of Immunosuppressive Agents—a Challenge for Therapeutic Drug Monitoring?

When using drugs for which TDM is not a common practice, treatment optimization is guided by the observed clinical effects and/or laboratory test results. When replacing the original preparation for such a drug with a generic one, we do not consider how the concentration of the drug in the blood changes, but carefully observe the clinical and biochemical effects. However, when dealing with a drug whose concentration is routinely monitored, we intuitively pay attention to changes in concentration and other pharmacokinetic parameters as a result of conversion, often forgetting the clinical evaluation of drug effects. This was a trap that needed to be avoided. For proper therapeutic management after conversion, possible scenarios must be defined as follows:

A. The drug concentration does not change significantly
   A1. Observed changes in clinical (biochemical) response, or
   A2. Clinical effect unchanged
B. The monitored drug concentration is significantly higher or lower than the original concentration
   B1. Observed changes in clinical (biochemical) response, or
   B2. Clinical effect unchanged

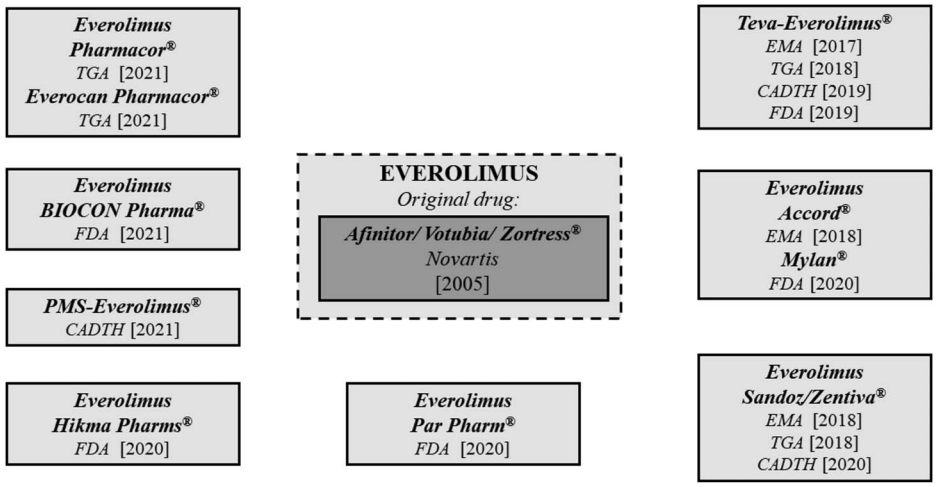

FIGURE 6. EVE generics scheme.

It seems obvious that case A2 alone does not require intervention. In case of B1, the drug dose needs to be adjusted, possibly due to "nonequivalent" bioavailability of the drug from the generic formulation in certain patients. What reaction should we take in the case of B2 when, despite the observed change in concentration, we do not see a change in the pharmacodynamic effect (or if it is too early to notice this change, eg, late transplant rejection)? Should we "treat" the concentration? Finally, the dose should be changed, and the concentration should be optimized when the clinical (biochemical) effect changes, whereas the concentration should remain within the therapeutic range (A1 case). This is probably related to the bioavailability of the drug after the administration of generic drugs, but we were not able to detect it in routine concentration monitoring. In addition, excipients in the drug formulation, nocebo effect, and the clinical condition of the patient during switching may also cause a nondetected difference in TDM.

As each ISD requires or benefits from (ie, MPA) therapeutic drug monitoring (TDM), a possible switch from one formulation to another with different pharmacokinetic parameters (although within an acceptable range) may finally lead to erroneous setting of an individually optimized dose. It is natural to maintain the same dose, which may be modified based on the concentrations measured after the switch. Safe conversion consumes time and money, thus generating additional costs for less expensive drugs.[5,13,63]

C_{min}

Bioequivalence studies are not meant to evaluate C_{min} even in a steady state. Steady-state trough concentrations are expected to be similar because of the similar AUC and C_{max}. When the latter is true, the laboratory should consider evaluating the correlation between routinely measured C_{min} values and pharmacokinetic parameters, such as AUC. This does not simply solve the issue of different C_{min} values between bioequivalent formulations because it is not rational to reassess the C_{min} therapeutic ranges of C_{min} based on the regression of C_{min} versus AUC for each generic drug. However, such knowledge is important for the interpretation of the TDM results.

C_2

Similar to C_{min}, C_2 was not assessed in the bioequivalence study. An additional disadvantage is the high intra- and interindividual variability that characterizes C_2. If monitoring is based on C_2 measurements, additional therapeutic monitoring care should be taken after conversion of the drug formulation.

$AUC_{0–12h}$

Only AUC and C_{max} were decisive in concluding BE. However, similar to single concentrations monitored at steady state (C_{min}, C_2, etc), $AUC_{0–12h}$ at steady state has not been evaluated in single-dose bioequivalence studies. In these cases, the $AUC_{0-\infty}$ or AUC_{0-t} ($AUC_{0–72h}$ is often used as an alternative for the latter) after a single drug administration is typically assessed. Thus, the $AUC_{0–12h}$ parameter monitored in some clinical centers (calculated using LSS) was not the same as that of the single-dose bioequivalence study.

AUC LSS

The algorithm obtained with one formulation will probably not function properly with another. This is because the pharmacokinetic profile is different for generic formulations, resulting in concentration changes at sampling points. PK profiles may be especially important during routine monitoring of through concentration of TAC—to identify overall exposure for drug. Monitoring of C_0 only may lead to false predictions of PK of TAC in individual case and, as consequence, provide an elevated risk for patients during immunosuppressive therapy.[46]

The adoption of previously prepared models in the case of immunosuppressive drugs must be thoroughly verified according to the generic formulation because there is a small amount of research and ignoring changes in drug formulation may lead to false predictions. Only Marquet et al studied population pharmacokinetics and Bayesian estimators of TAC and showed that PK models previously developed to original *Prograf* may be successfully used for generic formulations of TAC (even those with different t_{max} parameters).[64]

CONCLUSIONS

1. Any switch of formulations (generic for generic or generic for innovator) done without sufficient TDM (is essential to confirm/correct the appropriate ISD dosage) may represent an unacceptable risk for transplant patients.
2. Physicians, clinical pharmacists, and patients and their families should be educated about the nature and handling of generic ISDs and related safety and efficacy issues.
3. Generics are cheaper for health care system and using them in the pharmacotherapy is inevitable, but always with special prudence and based on TDM. The strike of a balance is still needed during switching.

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