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Generic Immunosuppression in Transplantation: A Controversial Analysis

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Abstract

Generic immunosuppressive drugs are available in Europe Canada and the United States. Between countries, there are large differences in penetration of generic drugs in general, and for immunosuppressive drugs in particular. The registration for generic immunosuppressive drugs are slightly different, but the criteria for registration of narrow therapeutic index drugs and bioequivalence studies, performed only in healthy volunteers, will remain in the medical landscape. About 50 studies compare the clinical eficacy and bioequivalence of the generic immunosuppressive drugs in patients with solid organ transplants. To allow for safe substitution, a number of criteria need to be fulfilled. Consensus statements were made by most transplant organizations. Authorities and payers should refrain from forcing pharmacists to dispense generic drugs in patients on maintenance immunosuppressive treatment. Generic substitution could be safe if realized by the treating physician, for a well-informed patient. Substitution must be followed by control visits to check if the patient is taking the medication correctly and if the drug exposure, through a close monitoring, remains stable. Substitution from one generic to another generic should be avoided, in all cases.

Keywords: Generic immunosuppression; Solid organ transplantation; Ethic; Substitution

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Introduction

Solid organ transplantation is one of the greatest medical advances of the twentieth century for patients with end stage organ dysfunction. In heart, liver and lung disease, transplantation represents the only alternative to death; for kidney and pancreas, transplantation represents an improvement in quality, as well as in duration of life. The number of successful organ transplantation, estimated in 2015 around 120,000 per year, with an increase of about 3 % [1,2] per year, worldwide, has increased in the past two to three decades due to improvement in surgical techniques and post transplant medical care. This medical success has been possible through the continuous innovation in immunosuppressive drugs, preventing graft rejection and improving survival outcomes following transplantation. Patients are required to take these drugs for the graft life span, balancing over and under-immunosuppression: an over-immunosuppression increases the risk for some of the side effects of transplantation including infectious complications, and malignancy, whereas an under-immunosuppression increases the risk for allograft rejection [3,4].

The immunosuppressive drugs are not cheap, all over the world: the monthly cost for an immunosuppressive regimen post organ transplantation may be between 2000 and 4000 US dollars per month, depending on the medications and doses utilized [5]. High costs may limit access to medications and influence medication adherence [5]. The cost to develop and market a new medication is extremely high, and following approval, innovator medications only remain under patent protection under 10 to 15 years [6]. Once the patency has expired, generic products may be approved and become available on the market.

Generic substitution has the potential for huge cost savings and is therefore an essential component to maintaining comprehensive and equitable healthcare, especially within public healthcare systems, often with limited resources. For certain classes of drugs, published studies show no difference in outcomes between the generic and innovator preparations and generic substitution is therefore not a concern [7]. For other drugs such as iron complexes, numerous publications underline variations in the eficacy and tolerance making the substitution dificult [8-12]. The substitution of

drugs with a narrow therapeutic index, such as immunosuppressive drugs, however, is more controversial. Before approval, each generic drug must show bioequivalence (the property wherein two drugs with identical active ingredients or two different dosage forms of the same drug possess similar bioavailability and produce the same effect at the site of physiological activity) to the innovator version in healthy adults, but there is no requirement to show bioequivalence or clinical eficacy in patients with transplanted organ. Over the past 15 years, different agencies have approved several generic immunosuppressants **(Table 1)**. Given that some of the immunosuppressive drugs require therapeutic drug monitoring and display a narrow therapeutic index, many transplant practitioners have dificulty in deciding whether innovator products can be safely replaced by generics [13]. In the transplant community this aspect led to the recommendation that patients and healthcare providers should pay careful attention to drug formulations and should monitor drug concentrations more often if a patient is switched to a generic preparation [14,15].

If patients and physicians remain doubtful of the equivalence of generic immunosuppressive drugs, this will limit the cost saving potential of these drugs from under prescription and more frequent laboratory monitoring when a generic is prescribed. We investigate the clinical eficacy, safety and bioequivalence of generic immunosuppressive drugs compared with innovator drugs in solid organ transplant recipients, and the position statement of various professional societies regarding the use of generic immunosuppressive drugs.

Generic drug approval process

Small-molecule drugs: A generic formulation is considered appropriate and qualified for approval in most countries if it demonstrates both pharmaceutical equivalence and bioequivalence when compared with the innovator product [16]. To achieve pharmaceutical equivalence, a generic medication should contain the same amount of the active ingredient, be available in similar dosage forms, given by the same route of administration, and meet the same or similar manufacturing standards. Innovator and generic products can differ in shape, size, packaging, scoring, additives (i.e., colors, preservatives, binders) and expiry dates [13]. Bioequivalence studies are typically performed in a small number of healthy volunteers, generally young and predominantly male. The FDA and EMA regulatory standards impose that the geometric mean with 90% CI (Confidence Interval) for these pharmacokinetic parameters must fall between 80 and 125%. One of the most common misconceptions about generic medications is regarding the range (80-125%) of variance in bioequivalence and this would allow the FDA and EMA to approve different medications that may vary in C_{max} and/or AUC by up to 45% (the difference between 80% and 125% is a 45% difference). However, given that the CI, and not the mean, must fit within the 80-125% limits, it is believed that any product differing from the innovator product by more than 13% will not meet bioequivalence standards [17]. Some of the generic drugs approved in the United States were

Table 1 Available maintenance immune-suppressants in Europe.

Drug	Generic Availability	Dosage forms	Trade Names	Generic Formulations	Patent expiration
Calcineurin inhibitors					
Cyclosporine	Yes	Capsule Solution IV solution	Sandimmun®	All	Expired
Cyclosporine modified	Yes	Capsule Solution	Neoral®	All	Expired
Tacrolimus	yes	Capsule			
		Capsule	Prograf®	only	Sep-19
		IV solution	Advagraf®		
Antiproliferatives					
Mycophenolate Mofetil	yes	Capsule Suspension IV Solution	Cell Cept®	All	Expired
Mycophenolic Acid		Tablet	Myfortic®	In some countries	Apr-17
Azathioprine		Tablet IV Solution	Imurel®	All	Expired
Corticosteroids					
Prednisone	Yes	Tablet	Cortancyl®	All	Expired
Target Rapamycin inhibitors					
Sirolimus	Yes	Tablet Solution	Rapamune®	Tablets in some countries	Nov-14
Everolimus	No	Tablet	Certican®	none	Nov-17
Costimulation blockade					
Belatacept	No	IV Solution	Nulojix®	none	Sep-21

analyzed secondarily and they differed by only 4.35 and 3.56%, respectively between approved generic and innovator products [17]. But none of narrow therapeutic index (NTI) drugs are concerned by these controls. Despite that immunosuppressive drugs are all under NTI designation, the FDA does not require more stringent bioequivalence parameters for these types of medications. Both Canadian Ministry of Health and EMA modified their bioequivalence standards for NTI drugs and required more stringent criteria for generic approval for this drug category, where concentration for AUC needs to fall between 90 and 112% instead of 80 and 125% [18,19].When the generic drug is formulated in a different dosage that the innovator product, it is no more in Europe a generic but an "hybrid" drug, without legal substitution.

Biosimilars: A biosimilar is simply defined as a biopharmaceutical protein designed to have active properties similar to an innovator biologic and approved through an abbreviated regulatory process [20].The EMA has had regulatory pathways for biosimilars since 2005 and currently there are 22 biosimilars approved by the EMA [20]. There are currently no EMA- or FDA-approved biosimilars with a transplant indication. However basiliximab lost its patent protection in most European countries in 2013 and the FDA currently lists the anti-thymocyte globulin products as eligible for bio-similarity studies.

Clinical data of generic immunosuppressive drugs used in organ transplantation

A number of about 50 publications have reported the use of

Table 2 Summary of included published studies [22].

Study (year)	Study Population	Study Protocole	Results
Cyclosporine			
Roza et al. [24]	50 stable kidney transplant recipients	Pts with Neoral®	PK interchangeable
		Then Pts switch to Gengraf®	Trough levels were similar
		Then Pts switch back to Neoral®	No significant dose adjustment were required
Carnahan et al. [25]	41 stable kidney transplant recipients	Pts were converted from Neoral® to Gengraf® and followed up for 1 year	Trough levels comparable
			No significant changes in serum creatinine
			No significant dose adjustment
			Cost-savings achieved
Taber et al. [26]	188 *de novo* kidney transplants recipients	100 Pts received Neoral®	Pts on Gengraf® experienced more rejection episodes and needed antibody treatment for rejection
		88 Pts received Gengraf®	
		Follow-up : 6 months	
Qazi et al. [27]	80 stable kidney transplant recipients	9 Pts remained on Neoral®	Significant changes in trough levels with Gengraf®
		73 Pts switched to Gengraf®	Trough levels moved back toward baseline after adjustment
		Follow-up of 4 weeks	
Vitko et al. [28]	99 stable kidney transplant recipients	52 Pts remained on Neoral®	Trough levels similar
		47 Pts received Equoral®	No significant differences in adverse events
		Follow-up for 6 months	Both formulations well tolerated
Tacrolimus			
McDevitt-Poter et al. [30]	70 stable liver or kidney transplant recipients	70 Pts were converted from Prograf® to Generic formulation	Tacrolimus C_0 did not differ significantly
			Pts on generics required more adjustments
			More than 50% decrease in monthly costs with generic
Momper et al. [31]	54 stable liver and kidney transplant recipients	54 Pts were converted from Prograf® to generic tacrolimus and followed up to 3 months	Generic tacrolimus was well tolerated
			Trough levels did not differ significantly
Rosenborg et al. [32]	63 stable kidney transplant recipients	63 Pts were converted to Generic formulation	C_0 and creatinine comparable before and after the switch
		Serum creatinine and trough levels performed three times during each period	23% decrease in drug cost per day achieved with generic formulation
Spense et al. [33]	234 stable liver, kidney or heart transplant recipients	234 Pts were converted from Prograf® to generic formulation of Tacrolimus	No significant changes in C_0 and creatinine
			More dose titration in few Pts
			Few Pts reverted back to Prograf®
			Decrease in drug cost with Generic formulation
			No deaths or allograft rejection

Alloway et al. [34]	68 stable kidney transplant recipients	2 periods of 14 days were 2 groups were on cross over	No difference in C_{max} C_0 et AUC
			No difference in rejection
			Similar adverse events
Hauch et al. [35]	39 stable kidney recipients under Generic formulation were compared with 159 Pts on Prograf®	Follow-up of 1 year	Trough levels need 5.2 *vs* 3.9 adjustment with Generic
		Were studied : doses adjustments, rejection, Mg and costs.	More perfusion of Mg (p<0.001)
			More rejection crisis (23.1% *vs* 10.2%)
			Global cost enhanced with Generic formulation
Mycophenolate Mofetil			
Sunder-Plassmann et al. [39]	43 stable kidney transplant recipients	Days 1-14 Pts received either Cell-Cept® or Myfenax®	AUC levels remained stable, C_{max} slightly outside of the range
		Days15-28 cross-over	Few adverse events
		Days 29-112 maintained regimen	
Rutkowski et al. [40]	303 stable kidney transplant regimen	First analysis Myfenac® (60Pts) *vs* Cell-Cept®(273Pts)	No difference in tranplant-related outcomes between Generic and Cell-Cept®
		Second analysis *de novo* Myfenac® (30 Pts) *vs* Cell-Cept® (30 Pts)	
Azathioprine			
Haroldson et al. [42]	30 heart transplant recipients	30 pts converted from Imuran® to generic formulation azathioprine	Similar safety and effcacy results
			Annual cost-savings reached US$318 per Pt

Pts: Patients; PK: Pharmacokinetics

generic immunosuppressants in solid organ transplant recipients, mainly renal transplants [21,22]. Studies included 17 randomized trials, 15 non-randomized, and 18 observational studies **(Table 2).**

Cyclosporine: The first generic approval came in 1998, and was removed two years later after demonstration that the release of the active ingredient was 20-30% lower when the product was mixed with apple juice [23]. In 2000 another generic version was approved: the manufacturer performed a prospective clinical trial; there were no statistically significant differences seen in pharmacokinetic parameters between originator and generic version. More importantly, the generic formulation exhibited a comparable eficacy and safety profile to the innovator drug [24]. Different studies were performed with the same version: one concluded to a significant cost-benefit following the conversion to the generic product [25]. Another study revealed, with the same generic, that despite similar concentration the generic product was associated with a higher rate of rejection (39 versus 25%, p=0.04) and subsequent rejection episodes (13% versus 4%, p=0.03) [26].

In 2006 a study underlines the importance of close monitoring following a generic conversion [27]. In 2010 another manufacturer conducted a multicenter, randomized trial comparing the eficacy and safety of both innovator and generic version, without any difference in outcomes or tolerability [28]. The same generic was used in heart transplant recipients without side effects and any adverse event observed after the conversion [29].

Tacrolimus: In August 2009 the first FDA-approved generic for tacrolimus was on the market. The first prospective observational trial concludes that converting from innovator to generic tacrolimus is safe and does carry a cost-benefit [30]. Nevertheless, a close monitoring is crucial as many patients require more dose adjustments following conversion [31]. It was the same in converting 103 stable renal and liver transplant recipients [32]. One of the largest study includes 234 stable patients (after kidney, liver or heart graft) converted to generic formulation: 15% of the patients required dose adjustments, and 2.4% were converted back to the innovator product [33].

A prospective randomized two-period, cross over pharmacokinetic analysis has been performed more recently, proving that this generic formulation of tacrolimus is bioequivalent to brand tacrolimus in stable renal transplant recipients [34,35]. Different batches of tacrolimus were also studied in children [36], elderly group of patients [37], switch de novo [38] liver transplant patients, without any difference. There are recently different formulations of tacrolimus which are hybrid forms of the drugs, including slow releasing forms, without real clinical studies, but theoretically without the possibility to be substituted by the pharmacist.

Mycophenolic acid (MPA): There are two formulations of MPA: mycophenolate mofetil and enteric-coated MPA. Both formulations are available as generics. Regardless of which agent is utilized, MPA itself has an intricate PK profile. MPA is not considered as a NTI drug, and the role of therapeutic drug monitoring in managing patient receiving these medications has revealed conflicting results. For both drugs AUC of 30-60mg.h/l (large range) was associated with lower rates of rejection.

The first generic formulation of mycophenolate mofetil received FDA approval end of 2008. In an international, multicenter randomized, open-label, study, the pharmacokinetic profile of the innovator product was compared with a generic in stable renal transplant recipients. There were some differences in the AUC, and the Cmax, but these results have been proven to have any impact on transplant outcomes [39]. Both products were well tolerated with comparable adverse effects [40]. Overall, it appears that generic mycophenolate mofetil has demonstrated similar eficacy and safety profiles compared with the innovator product.

The first enteric-coated MPA generic formulation was approved by the FDA in 2012. There are today no study in Europe and United States comparing generic enteric-coated MPA, to the innovator product. A Mexican study concludes that bioequivalence was not met and that the tested generic product should not be used in transplant recipients [41].

Azathioprine: Azathioprine is one of the oldest immunosuppressants used for allograft rejection prevention. Routine dosage is not required with azathioprine. Doses are generally based on body weight. Thus, small fluctuations in the pharmacokinetic parameters of azathioprine should not be problematic. The first generic azathioprine formulation was launched in 1996, despite this agent loses its patent protection in 1979. There is only one study in heart transplant recipients [42].

Sirolimus: The first generic sirolimus product was FDA-approved on September 2014, with an approval for only tablets. Studies comparing innovator sirolimus to its generic formulation have not yet been published, except in China [43].

The balance between over- and under-immunosuppression is a fine line for most, especially early after transplantation. Some confounding factors in this balancing act may be the use of generic immunosuppressants and the potential from generic-to-generic throughout the transplant process. There is a decided drug acquisition cost-benefit when using generic immunosuppressants, which may improve medication access and adherence. The majority of the data with generic immunosuppressants demonstrate their eficacy and safety, when used de novo and for conversion in patients maintained on an innovator product, but conversion must be realized by the transplant team, and not changed thereafter.

Position statements on generic immunosuppressive drugs

In response to the concern of transplant clinicians over the use of generic immunosuppressants, many national and international societies and transplant organizations have formed and published opinion statements regarding this issue.

American Society of Transplantation: The American Society of Transplantation published in 2003 a summary of a meeting [44]. Participants strongly supported efforts to offer less expensive medications, hoping to improve compliance. Most agreed that the prescription of generic immunosuppressive drugs de novo was safe in low-risk transplants patients. Some expressed concerns about uncontrolled substitutions, and there were a strong support for bioequivalence studies in at-risk subpopulations.

International Society for Heart and Lung Transplantation: Their committee suggests, in 2009, that in some clinical situations, generic substitution could be used, if frequent monitoring is instituted following conversion to a generic [45]. They also suggested increased patient education regarding appearance or labeling of the generic drugs, to signify the need for closer controls if the patient receive a different brand of immunosuppressive drug. This society also stipulated that, under certain clinical conditions, transplant practitioners should use generic immunosuppressants with extreme caution [46].

European Society for Organ Transplantation: In 2011, this society took the position that the choice of converting between innovator and generic immunosuppressants should be limited to specialized transplant physicians [14]. They were satisfied with the stricter criteria used by the European Medicine Agency. They also stated that any conversion to a generic should be accompanied by strict follow-up and monitoring to asses that adequate therapeutic levels are met, and that conversion to generic products should be avoided early after transplant because of a higher risk of rejection. They urged practitioners to avoid switching among generic formulations, and if a conversion is decided the same generic should be given to the patients [14].

Canadian Society of Transplantation:

In 2012, this society noted that there is a lack of data and literature regarding the safety and eficacy of generic immunosuppressants [47], and stressed that there is a need for more strict regulatory principles. They asked for bioequivalence to be demonstrated, not only in healthy adults, but also in transplant recipients and in subpopulations known to have a high variability in blood concentration. Finally they also stressed the involvement of pharmacists in providing education for patients, and to deliver to the patient always the generic drug from the same manufacturer [47]. It was the same for the French Society of Transplantation [48].

Real-life scenarios

When a company tests a new generic medication, it is only required to be tested against the innovator product. None of the regulatory agencies require one generic medication to demonstrate bioequivalence with any other approved generic formulation [49]. In such cases all generic formulations are deemed interchangeable. This is certainly a potential shortcoming of the current generic approval process. Unfortunately for clinicians, without generic-to-generic bioequivalence data, and the great probability that generic-to-generic conversions will take place at the pharmacy level, at each monthly prescription, with sometimes the combination of different generics in the same delivery, it is dificult to determine when to institute more aggressive monitoring in maintenance transplant recipients.

Given that generic-to-generic conversion is likely what happens

Table 3 Key points in the use of generic immunosuppressive drugs in solid organ transplantation.

Key Points
• Generic immunosuppressants have been available in the global market place for more than 20 years.
• Generics are only required to prove pharmaceutical equivalence and bioequivalence approval by regulatory authorities.
• Pharmaceutical equivalence means having the same amount of the active ingredient and in similar dosages, being given by the same route of administration, and meet the same or similar manufacturing standards.
• Bioequivalence depicts the rate and extend to which the active ingredient reaches the systemic circulation by measuring area under the curve (AUC) and C_{max} of both the generic and the innovator products in healthy volunteers.
• Bioequivalence standards according to the US FDA require that the geometric mean with 90% CI for the AUC and C_{max} fall between 80% and 125% for all medicines.
• Both the EMA and the Canada recognize that narrow therapeutic index drugs should have stricter bioequivalence ranges and require generic narrow therapeutic index products, with C_{max} between 90% and 112% of the innovator product.
• Biosimilars are not yet available for any biopharmaceutical with a transplant indication.
• Very few well-designed clinical or pharmacokinetic studies are available regarding the use of a generic immunosuppressant in a solid organ transplant population.
• The data that are available point the fact that generic immunosuppressants appear to be equally safe and effective compared with innovator product, but require close monitoring when converting a patient from a brand product to a generic.
• Several transplant organizations have create consensus statements regarding immunosuppressants and generally support their use under controlled conditions where therapeutic drug monitoring is utilized to monitor patients' response to a generic.
• One concern that remains in the transplant community is the potential for generic-to-generic conversions at the pharmacy level that might necessitate intensified monitoring or be done without notification to the patient or prescriber.

in real-life scenarios, and the current literature only has studies where one generic formulation is compared with the innovator product, a six-way cross-over study was recently designed, whereby patients are converted not only between innovator and generic tacrolimus, but also between five different generic tacrolimus formulations [50]. This study will represent the type of real world situation where patients can be dispensed different generic tacrolimus formulation depending what is in stock at their pharmacy at the time their prescription is filled. The recruitment was stopped in March 2016. First results were recently published: equivalence between tacrolimus innovator and two generic products as well as between two generic products in individuals after kidney or liver transplantation following current FDA bioequivalence metrics; bioequivalence for the NTI provides evidence that generic products that are bioequivalent with the innovator product are also bioequivalent to each other. One generic product do not met the EMA acceptance criteria for NTI [51].

Conclusion

The role of the immunosuppressive agents in the improvements in transplant outcomes over the past three decade is undeniable **(Table 3)**. The registration of generic immunosuppressive drugs is not going to change in the next ten years, although the transplant community has request to do so [52]. Bioequivalence studies, performed in healthy volunteers and not in transplant patients, will remain the backbone of the registration process. There is a decided drug acquisition cost-benefit when using generic immunosuppressants which may improve medication access and adherence. The majority of the data with generic immunosuppressants demonstrate their eficacy and safety both when used de novo and for conversion in transplanted patients [53,54], with a cost benefit effect. The first substitution should realized on the initiative of the transplant team with consent of the patient. Therapeutic activity should be controlled carefully thereafter. After the first switch from innovator to generic under the conditions mentioned above, no further substitution from one generic to another should be performed. Therefore for the first substitution it is better to prescribe a branded generic specifying which formulation should be dispensed to the patient; the successive one should be the same one. Health insurance agencies and other payers should not force pharmacists to deliver any generic formulation to patients, but always the same one. Bioequivalence should not be interpreted as drugs being identical, and it is not true that patients can unconditionally switched from one generic formulation to another [55,56].

High quality data showing bioequivalence and clinical eficacy of generic immunosuppressants in solid organ transplants are lacking. Well designed, randomized controlled trial comparing clinical end-points are unlikely to be performed because of the large sample sizes that would be needed and the additional costs. What may be more easily obtained is that switching from one generic formulation to another should be prohibited. Only the, generic controlled substitution will be safe. Transplant practitioners must act now to create personal-or institution-specific protocols on how to manage the de novo use or conversion to generic and biosimilars in solid organ transplantation: generics in transplantation are not going away.

References

1 https://issuu.com/o-n-t/docs

2 https://www.france-adot.org/

3 Karam S, Wali RK (2015) Current state of immunosuppression: Past, Present and Future. Crit Rev Eukaryot Gene Exp 25: 113-134.

4 Lee RA, Gabardi S (2012) Current trends in immunosuppressive therapies for renal transplant recipients. Am J Health Syst Pharm 69: 1961-1975.

5 Perrottet N, Aubert V Venetz JP, Ugolini E, Matter M, et al. (2013) Evolving trends in the costs associated with hospital use of immunosuppressive drugs. Transplantation 95: e24-e25.

6 https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/bioavailability-bioequivalence/comparative-bioavailability-standards-formulations-used-systemic-effects.html

7 Rottembourg J, Nasica-Labouze J (2015) The implementation of generics in France. GaBi J 4: 36-42.

8 Rottembourg J, Kadri A, Leonard E, Dansaert A, Lafuma (2011) A Do two intravenous iron sucrose preparations have the same eficacy? Nephrol Dial Transplant 26: 3262-3267.

9 Stein J, Dignass A, Chow AK (2012) Clinical case reports raise doubts about the therapeutic equivalence of an iron sucrose similar preparation compared with iron sucrose originator. Curr Med Res Opin 28: 241-243.

10 Martin-Malo A, Merino A, Carracedo J, Alvarez-Lara MA, Ojeda R, et al. (2012) Effect of intravenous iron sucrose on mononuclear cells during haemodialysis session. Nephrol Dial Transplant 27: 2465-2471.

11 Lee ES, Park BR, Kim JS, Choi GY, Lee JJ, et al. (2013) Comparison of adverse event profile of intravenous iron sucrose and iron sucrose similar in postpartum and gynaecologic operative patients. Curr Med Res Opin 29: 141-147.

12 Agüera ML, Martin-Malo A, Alvarez-Lara MA, Garcia-Montemayor VE, Canton P, et al. (2015) Eficiency of original versus generic intravenous iron formulations in patients on Haemodialysis. PLOS One 10: 0135967.

13 Matas AJ, Smith JM, Skeans MA, Thompson B, Gustafson SK, et al. (2015) OPTN/SRTR 2013 Annual data Report: Kidney AM J Transplant 15: S21-34.

14 Van Gelder T, ESOT Advisory Committee on Generic Substitution (2011) European Society for Organ Transplantation. Advisory Committee Recommendations on Generic Substitution of Immunosuppressive Drugs. Transplant Int 2011; 24:1135-1145.

15 Klintmalm GB (2011) Immunosuppression, generic drugs and the FDA. Am J Transplant. 11: 1765-1766.

16 Code de la Santé Publique, article L 5121-1, modifié par la loi n° 2013-1203 du 23 décembre 2013, article 47.

17 Davit BM, Nwakama PE, Buehler GJ, Conner DP, Haïdar SH, et al. (2009) Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States food and drug administration. Ann Pharmacother 43:1583-1597.

18 www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/gd_standards _ld_ normes-eng.php

19 https://www.ema.europa.eu/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf

20 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/

21 Molnar AO, Fergusson D, Tsampalieros AK, Bennett A, Fergusson N, et al. (2015) Generic immunosuppression in solid organ transplantation: systematic review and meta-analysis. BMJ 350: h3163.

22 El Hajj S, Kim M, Phillips K, Gabardi S (2015) Generic immunosuppression in transplantation: current evidence and controversial issues. Expert Rev Clin Immunol 11: 659-672.

23 www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm173083.htm

24 Roza A, Tomlanovich S, Merion R, Pollak R, Wright F, et al. (2002) Conversion of stable renal allograft recipients to a bioequivalent cyclosporine formulation. Transplantation 74: 1013-1017

25 Carnahan W, Cooper TY (2003) Neoral-to-Gengraf conversion in renal transplant recipients. Transplant Proc 35: 1308-1313.

26 Taber DJ, Baillie GM, Ashcraft EE, Rogers J, Lin A, et al. (2005) Does bioequivalence between modified cyclosporine formulations translate into equal outcomes. Transplantation 80: 1633-1635.

27 Qazi YA, Forrest A, Tornatore K, Venuto RC (2006) The clinical impact of 1:1 conversion from Neoral to a generic cyclosporine (Gengraf) in renal transplant recipients with stable graft function. Clin Transplant 20: 313-317.

28 Vitko S, Ferk M (2010) Interchangeability of cyclosporine formulations in stable adult renal transplant recipients: comparison of Equoral and Neoral capsules in an international, mulicenter, randomized, open label trial. Kidney Int Suppl 115: S12-S16.

29 Kraueter M, Helmschrott M, Erbel C, Gleissner CA, FrankensteinL, et al. (2013) Conversion to generic cyclosporine A in stable chronic patients after heart transplantation. Drug Des Devel Ther 7: 1421-1426.

30 McDevit-Potter LM, Sadaka B, Tichy EM, Rogers CC, Gabardi S (2011) A multicenter experience with generic tacrolimus conversion. Transplantation 92: 653-657.

31 Momper JD, Ridenour TA, Schonder KS, Shapiro R, Humar A, et al. (2011) The impact of conversion from prograf to generic tacrolimus in liver and kidney transplant recipients with stable graft function. Am J Transplant 11: 1861-1867.

32 Rosenborg S, Nordström A, Almquist T, Wennberg L, Barany P (2014) Systematic conversion to generic tacrolimus in stable kidney transplant recipients. Clin Kidney J 7: 151-155.

33 Spence MM, Nguyen LM, Hui RL, Chan J (2012) Evaluation of clinical and safety outcomes associated with conversion from brand-name to generic tacrolimus in transplant recipients enrolled in an integrated health care system. Pharmacotherapy 32: 981-987.

34 Alloway RR, Sadaka B, Trofe-Clark J, Wiland A, Bloom RD (2012) A randomized pharmacokinetic study of the generic tacrolimus versus reference tacrolimus in kidney transplant recipients. Am J transplant 12: 2825-2831.

35 Hauch A, John M, Smith A, Dortonne I, Patel U, et al. (2015) Generics: are all immunosuppression agents created equally? Surgery 158: 1049-1055.

36 Abdulnour HA, Araya CE, Dharnikadharha VR (2010) Comparison of generic tacrolimus and Prograf drug levels in a pediatric kidney transplant program: brief communication. Pediatr Transplant 14: 1007-1011.

37 Robertsen I, Asberg A, Ingero AO, Vethe NT, Bremer S, et al. (2015) Use of generic tacrolimus in elderly renal transplant recipients: precaution is needed. Transplantation 99: 528-532.

38 Dannhorn E, Cheung M, Rodrigues S,Cooper H, Thorburn D, et al. (2014) De novo use of generic tacrolimus in liver transplantation- a single center experience with one-year follow-up. Clin Transplant 28: 1349-1357.

39 Sunder-Plassman G, Reinke P, Rath T, Wiecek A, Nowicki M, et al. (2012) Comparative pharmacokinetic study of two mycophenolate mofetil formulations in stable kidney transplant recipients. Transplant Int 25: 680-686.

40 Rutkowski B, Bzoma B, Debska-Slizien A, Chamienia A (2014) Generic formulation of mycophenolate mofetil (Myfenax) in de novo renal transplant recipients: results of 12-month observation. Transplant Proc 46: 2683-2688.

41 Esquivel A, Gonzales-Ramirez R, Alberu J, Gracida C, Medeiros M, et al. (2010) Comparison of dissolution properties of 2 enteric coated formulations containing mycophenolate sodium: Myfortic vs Femulan. Transplant Proceed 42: 353-356.

42 Haroldson JA, Somerville KT, Carlson S, Hanson J, Emery RW, et al. (2001) A retrospective assessment of safety, eficacy, and pharmacoeconomics of generic azathioprine in heart transplant recipients. J Heart Lung Transplant 20: 372-374.

43 Huang MZ, Chen JC, Hu XJ, Liu J, Wu GL, et al. (2013) Comparative bioavailability and pharmacokinetics of sirolimus tablets in healthy Chinese volunteers. Int J Clin Pharmacol Ther 51: 816-822.

44 Alloway RR, Isaacs R, Lake K, Hoyer P, First R, et al. (2003) Report of the American Society of Transplantation conference on immunosuppressive drugs and the use of generic immunosuppression. Am J Transplant 3: 1211-1215.

45 Uber PA, Ross HJ, Zuckerman AO, Sweet SC, Corris PA, et al. (2009) Generic drug immunosuppression in thoracic transplantation: an ISHLT educational advisory. J Heart Lung Transplant 28: 655-660.

46 Kasike BL, Zeier MG, Chapman JR, Craig JC, Ekberg H, et al. (2010) KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. Kidney Int 77: 299-311.

47 Harrison JJ, Schiff JR, Coursol CJ, Daley CJA, Dipchand AI, et al. (2012) Generic immunosuppression in solid organ transplantation: a Canadian perspective. Transplantation 93: 657-665.

48 Le Meur Y, Sebbag L, Anglicheau D, Kamar N, Billaud E, et al. (2014) Recommandations de la Société francophone de transplantation sur l'utilisation des génériques des immunosuppresseurs. Courrier de la Transplantation. 14: 129.

49 www.accessdata.gov/scripts/cder/ob/default.cfm

50 https://clinicaltrials.gov/ct2/show/NCT02014103

51 Alloway RR, Vincks AA, Fukuda T, Mizumo T, King EC, W et al (2017) Bioequivalence between innovator and generic tacrolimus in liver and kidney transplant recipients: a randomized, crossover clinical trial. PLoS Med 14:e1002428.

52 Al Ameri MN, Whittaker C, Tucker A, Yaqoob M, Johnston A (2011) A survey to determine the views of renal transplant patients on generic substitution in the UK. Transplant Int 24: 770-779.

53 Hulbert AL, Pilch NA, Taber DJ, Chavin KD, Baliga PK (2012) Generic immunosuppression deciphering the message our patients are receiving. Ann Pharmacother 46: 671-677.

54 Allard J, Fortin MC (2014) Is it ethical to prescribe generic immunosuppressive drugs to renal transplant patients. Can J of Kidney Health Disease 1: 23.

55 Ensor CR, Trofe-Clark J, Gabardi S, Mc Devitt-Potter LM, Shullo MA (2011)Generic maintenance immunosuppression in solid organ-transplant recipients. Pharmacotherapy 31: 1111-1129.

56 Johnston A (2013) Equivalence and interchangeability of narrow therapeutic index drugs in organ transplantation. Eur J Hosp Pharm Sci Prat 20: 302-307.