Bioavailability, Efficacy and Safety of Generic Immunosuppressive Drugs for Kidney Transplantation: A Systematic Review and Meta-Analysis

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Key Words

Drug · Immunosuppressant · Cyclosporine · Tacrolimus · Mycophenolate mofetil · Generic · Test · Brand · Reference · Bioequivalence · Efficacy · Safety · Kidney · Transplant

Abstract

Background: Concerns exist over the extrapolation of bioavailability studies of generic immunosuppressive drugs in healthy volunteers, regarding their efficacy and safety in kidney transplant recipients. We conducted a meta-analysis of trials examining the bioavailability of generic (test) immunosuppressive drugs relative to their brand (reference) counterparts in healthy volunteers, based on the US Food and Drug Administration requirements for approval of generics, and their efficacy and safety in kidney transplant recipients. **Methods:** Eligible studies were identified in PubMed, Cochrane Central Register of Controlled Trials, Scopus, ClinicalTrials.gov, and conference abstracts. **Results:** Twenty cross-over trials of healthy volunteers ($n = 641$) and 6 parallel-arm randomized controlled trials of kidney transplant recipients

($n = 594$) were identified. The 90% CI of the pooled test-to-reference drug ratio for maximum or peak plasma concentration ($C_{\max}$) and area under the plasma concentration time-curve from time 0 to time of last determinable concentration ($AUC_{(0-t)}$) fell within the required range (0.80–1.25) for cyclosporine ($C_{\max}$ 0.91; 90% CI 0.86–0.95; and $AUC_{(0-t)}$ 0.97; 90% CI 0.94–1.00), tacrolimus ($C_{\max}$ 1.17; 90% CI 1.09–1.24; and $AUC_{(0-t)}$ 1.00; 90% CI 0.97–1.03) and mycophenolate mofetil ($C_{\max}$ 0.98; 90% CI 0.96–1.01; and $AUC_{(0-t)}$ 1.00; 90% CI 0.99–1.01). In subgroup analyses, some generic cyclosporine formulations did not meet criteria for bioequivalence. No significant differences were observed in the time to maximum plasma concentration and terminal plasma half-life between generic and brand drugs. In parallel-arm trials, generic cyclosporine was non-inferior to brand counterpart in terms of acute allograft rejection, infections, and death. **Conclusions:** Not all generic immunosuppressive drugs have similar relative bioavailability to their brand name counterparts. Evidence on their efficacy and safety is inconclusive. Tighter regulatory requirement for approval of generic drugs with narrow therapeutic index is needed. © 2016 S. Karger AG, Basel

Introduction

Kidney transplantation for end-stage renal disease (ESRD) is associated with improved survival and quality of life, and health care cost reduction. In the United States, 30% of ESRD patients have a functioning kidney transplant [1], with annual per-patient cost for immunosuppressive medications estimated at \$15,000–20,000 [2]. Under current Medicare policy, kidney transplant recipients lose coverage 36 months after transplantation, incurring the annual cost of immunosuppressive drugs thereafter. Considering that cost is an important determinant of medication nonadherence, it is not surprising that long-term kidney allograft survival rates in the United States are substantially lower compared to other developed countries, where lifetime access to immunosuppressive drugs is a right [2–4].

In an effort to reduce drug-related costs, generic substitutes have been introduced into the market [5]. Concerns, however, exist over the extrapolation of bioequivalence studies of generic immunosuppressive drugs in healthy volunteers, regarding their efficacy and safety in organ transplant recipients. For instance, there are reports of variability in the absorption of generic cyclosporine between healthy subjects and organ transplant recipients [6], and kidney transplant recipients receiving generic cyclosporine require higher doses or alternate immunosuppressive drugs [7]. Furthermore, the recall of an approved generic cyclosporine oral solution after a post-approval study had indicated non-bioequivalence to its brand counterpart, calls into question the generic drug approval process [8].

To summarize the available evidence, inform clinical practice, and provide future research directions, we performed a systematic review and meta-analysis of trials examining the bioavailability of generic immunosuppressive drugs, available worldwide, in healthy volunteers, based on the US Food and Drug Administration (FDA) requirements for approval of generics, focusing on cyclosporine, tacrolimus, and mycophenolate mofetil (MMF); we also reviewed the evidence on their efficacy and safety in kidney transplant recipients, relative to their brand counterparts.

Methods

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (online suppl. eTable 1; for all online suppl. material, see www.karger.com/doi/10.1159/000449020) [9].

Data Sources and Searches

The literature search and study selection were performed independently by 2 authors (N.R.G. and E.T.). The following electronic databases were searched for relevant citations (online suppl. eTable 2): PubMed, Scopus, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov (inception to January 2015). Bibliographies of retrieved articles were inspected, and abstracts from scientific meetings of the American Transplant Society and American Society of Nephrology (up to 2014) were searched. The search strategy was limited to human studies with no restrictions on language, sample size, duration of study, or year of publication.

Study Selection

We followed the US FDA Guidance to Industry document on bioavailability and bioequivalence studies for orally administered drugs to identify relevant trials examining the relative bioavailability of generic to brand immunosuppressive drugs [10]. We searched for crossover trials independent of the number of study periods, and included trials of adults with a washout period of more than 5 half-lives, in accordance with the FDA guidance.

Regarding the efficacy and safety profile of generic relative-to-brand immunosuppressive drugs, we selected parallel-arm randomized controlled trials comparing the 2 formulations in kidney transplant recipients.

Data Extraction and Risk of Bias Assessment

Two authors (N.R.G. and E.T.) independently extracted data and assessed risk of bias using the Cochrane's Collaboration tool [11]. The tool evaluates 6 domains of bias (selection, performance, detection, attrition, reporting, and other). Three additional domains deemed appropriate for crossover study design were added (suitability of crossover design, random order of treatment assignment, and presence of carry-over effect). Each domain's risk of bias was assessed as low, high or unclear. Disagreements were resolved in consultation with a third author (B.L.J.). Authors of 4 trials were contacted for additional information.

The following data were extracted from crossover trials: country of origin, year of publication, health status, fasting state, study design, name of brand and generic immunosuppressant, drug formulation, washout and study period, drug dose, drug measurement assay, characteristics of study participants (gender, mean age, and weight), and outcomes of interest. From parallel-arm trials, the following additional data were extracted: kidney transplant type (deceased or living donor), time from transplantation, concomitant immunosuppressants, and study period.

The pharmacokinetic parameters of interest extracted from crossover trials included the mean area under the plasma concentration time-curve from time 0 to time of last determinable concentration ($AUC_{(0-t)}$), maximum or peak plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and terminal plasma half-life ($T_{1/2}$) of the drug. For each parameter, the mean and SD of the test (generic) and reference (brand) drug was extracted. We also extracted or derived the arithmetic mean test-to-reference (T/R) drug ratio (i.e., generic-to-brand ratio) for the $AUC_{(0-t)}$ and C_{max} , with the standard deviation and 90% CI [10]. For MMF, we extracted data on mycophenolic acid, the active metabolite that represents a better method of drug monitoring. Values reported as median with range were converted to mean with SD [12].

Fig. 1. Study selection flow diagram.

The safety and efficacy endpoints of interest extracted from parallel-arm trials included episodes of kidney allograft rejection, infections, adverse events (AEs), serious or severe AEs (SAEs), and death.

Data Synthesis and Analysis

The pharmacokinetic parameters were analyzed in accordance with the FDA guidance on bioavailability and bioequivalence studies of generic drugs [10]. For each immunosuppressant, random-effects model meta-analyses were performed to compute the pooled weighted T/R drug ratio for the $AUC_{(0-t)}$ and C_{max} with the 90% CI. Most trials reported arithmetic mean ratios with the corresponding 90% CI. When geometric mean values were reported, we calculated the arithmetic mean ratio (with the corresponding 90% CI) using a Taylor series approximation method [13]. When data for $AUC_{(0-t)}$ and C_{max} were reported as geometric mean ratios, we used arithmetic mean data reported individually for the test and reference drug, and re-calculated the pooled arithmetic mean ratio with the 90% CI [13]. Pharmacokinetic parameters between the test and reference drug were deemed bioequivalent if the ratio of the mean values with the 90% CI fell within the 0.80–1.25 range, in accordance with FDA guidelines [10]. For T_{max} and $T_{1/2}$, random-effects model meta-analyses were performed to calculate the weighted mean difference (WMD) of the reference and test drug with the 95% CI.

Due to the low number of events, Peto fixed-effect model meta-analyses were used to calculate pooled ORs with 95% CI for the binary endpoints.

Existence of heterogeneity among study effect sizes was examined using the I^2 index and the chi-square test p value. An I^2 index $\geq 50\%$ indicated moderate-to-high heterogeneity [14]. To investigate heterogeneity, we conducted subgroup analyses comparing the brand drug with each generic formulation. All

analyses were performed using version 13 of the Stata® Data Analysis and Statistical Software (StataCorp LP, College Station, Tex., USA).

Results

Study Characteristics

Potentially relevant citations, numbering 25,535 were identified and screened (fig. 1). Ninety-eight articles were retrieved for evaluation, of which 23 (26 trials) provided analyzable data [15–37]. Seventeen articles investigated relative bioavailability of generic to brand immunosuppressants, predominantly in healthy volunteers (table 1) [15–31]. No generic formulation identified in studies of healthy volunteers was approved for use in the United States. Six parallel-arm trials of kidney transplant recipients investigated the efficacy and safety of generic relative to brand immunosuppressants, of which only 2 (Equoral® and Gengraf®) were approved for use in the United States (table 2) [15, 32–36].

The relative bioavailability of generic cyclosporine was studied in 12 crossover trials and sub-studies [17, 19, 20, 23, 24, 28–31, 37]. Trials varied in sample size (12–34 subjects). With the exception of one trial of dialysis patients [29], the populations largely consisted of healthy adults. Neoral® was compared to generic Sigmasporin-

Table 1. Characteristics of the bioequivalence crossover randomized controlled trials of healthy subjects included in the meta-analysis

Author	Year	Country	Number of subjects	Age, years [†]	Men, %	Weight, kg	Generic immunosuppressant (manufacturer, country)	Oral formulation	Dose administered	Sampling interval, h	Washout period, days	Drug measurement assay	Lower limit of detection	Pharmacokinetic parameters
<i>Neoral</i> [®]														
Sachdeva et al. [28]	1997	India	12	17–35	100	50–79	NR (Panacea Biotech Ltd., India)	Solution	15 mg/kg	24	7	HPLC	NR	C_{max} , $AUC_{(0-24)}$, $AUC_{(0-\infty)}$, $T_{1/2}$, T_{max}
Tanasescu et al. [30]	1999	Romania	24	21–40	50	52–90	Sigmasporin Microoral (Sigma Pharma, Brazil)	NR	2.5 mg/kg	24	14	HPLC	NR	C_{max} , $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, T_{max}
Najib et al. [24]	2003	Jordan	30	25	NR	71	Sigmasporin Microoral (Gulf Pharmaceutical Industries, UAE)	Capsule	100 mg	24	7	HPLC-MS	5.0 ng/ml	C_{max} , $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $T_{1/2}$, T_{max}
Talaulikar et al. [29]*	2003	India	30	34	83	50	Arpimmune ME (RPG Life Sciences Ltd., India)	Capsule	4 mg/kg	–	7	RIA	NR	C_{max} , $AUC_{(0-t)}$, T_{max}
Mendes et al. [23]	2004	Brazil	22	32	100	77	Sigmasporin Microoral (Sigma Pharma, Brazil)	Capsule	200 mg	12	7	FPAI	21.8 mg/ml	C_{max} , $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $T_{1/2}$, T_{max}
Kees et al. [20]	2004	USA	12	27 (22–32)	100	74	Cicloral (Hexal AG, Germany)	Capsule	200 mg	48	7	HPLC	15 ng/ml	C_{max} , $AUC_{(0-\infty)}$, $T_{1/2}$, T_{max}
Kees et al. [19] [†]	2006	Germany	12	25 (22–29)	100	72	Cicloral (Hexal AG, Germany)	Capsule	100 mg	48	7	HPLC	15 ng/ml	C_{max} , $AUC_{(0-\infty)}$, $T_{1/2}$, T_{max}
			12	26 (23–30)		78		Capsule	300 mg	48	7			
			12	26 (24–30)		74		Capsule	600 mg	48	7			
Avramoff et al. [17]	2007	Israel	24	19–40	100	NR	Deximune (Dexel Pharma Ltd., Israel)	Capsule	200 mg	24	7	FPAI	50 mg/ml	C_{max} , $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $T_{1/2}$, T_{max}
Piñeyro-López et al. [37]	2009	Mexico	34	22 (18–29)	NR	78	Zaven ME (RPG Life Sciences Ltd., India, imported by Gelpharma, S.A. de C.V., Mexico)	Capsule	100 mg	48	14	HPLC-MS	10 ng/ml	C_{max} , $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $T_{1/2}$, T_{max}
Wu et al. [31]	2012	China	24	NR	100	NR	NR (Sinopharm Chuankang Pharmaceutical Co., Ltd., China)	Capsule	400 mg	48	7	HPLC-UV		C_{max} , $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $T_{1/2}$, T_{max}
<i>Prograf</i> [®]														
Park et al. [25]**	2007	South Korea	29	29	76	66	Tacrobell [®] (Chong Kun Dang, Seoul, Korea)	Capsule	2 mg	96	21	LC/MS/MS	0.5 ng/ml	C_{max} , $C_{min0-24}$, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $AUC_{(0-24)}$, C_{96}

Table 1. (continued)

Author	Year	Country	Number of subjects	Age, years [†]	Men, %	Weight, kg	Generic immunosuppressant (manufacturer, country)	Oral formulation	Dose administered	Sampling interval, h	Washout period, days	Drug measurement assay	Lower limit of detection	Pharmacokinetic parameters
Mathew et al. [22]	2011	India	36	27	100	61	NR (Intas Pharmaceuticals Ltd., Gujarat, India)	Capsule	0.5 mg	72	20	LC-MS/MS	39.99 pg/ml	C_{max} , $AUC_{(0-72)}$, $AUC_{(0-\infty)}$, $T_{1/2}$, T_{max}
CellCept® Masri et al. [21]	2007	Czech Republic	24	28 (6)	83	77	MMF 500 (Medis Laboratories, Tunisia)	Tablet	500 mg	24	8	HPLC	NR	C_{max} , $AUC_{(0-4)}$
Almeida et al. [16] ^{††}	2010	Spain, Québec	100	38	62	68	NR (Grupo Tecnimede, Portugal)	Tablet	500 mg	48	14	LC-MS/MS	19.95 ng/ml	C_{max} , $AUC_{(0-4)}$, $AUC_{(0-\infty)}$, $T_{1/2}$
Estevez-Carrizo et al. [18]	2010	Uruguay	24	26	100	72	Suprimum 500 (Laboratorios Clausen S.A., Uruguay)	Tablet	500 mg	36	7 weeks	HPLC	NR	C_{max} , $AUC_{(0-32)}$, $AUC_{(0-\infty)}$, T_{max}
Patel et al. [26]	2011	India	116	28	100	59	NR (Intas Pharmaceuticals Ltd., India)	Tablet	500 mg	60	14	LC-MS/MS	75.43 ng/ml	C_{max} , $AUC_{(0-4)}$, $AUC_{(0-\infty)}$, $T_{1/2}$, T_{max}
Saavedra et al. [27]	2011	Chile	22	28	100	75	Linfonex (Laboratorios Recalcine S.A., Chile)	Tablet	1,000 mg	12	10	HPLC	0.3 µg/ml	C_{max} , $AUC_{(0-12)}$, $AUC_{(0-\infty)}$, T_{max}

* Multi-dose trial with participants on maintenance hemodialysis awaiting kidney transplantation; ** participants were administered 2 doses of each drug on the same day (morning and evening) and drug levels were measured 96 h after the first dose.

[†] 3-period crossover trial; ^{††} 4-period crossover trial; mean and/or range; all the trials were conducted in volunteers who were in a fasting state with the exception of one trial where the drug was administered with mango juice [28].

HPLC = High-performance liquid chromatography; MS = mass spectrometry; FPAI = fluorescence polarization immunoassay; RIA = radioimmunoassay; $AUC_{0-\infty}$ = area-under-the-curve to infinite time; NR = not reported; None of the generic immunosuppressants shown in the table are approved for use in the United States.

Table 2. Characteristics of the parallel-arm randomized controlled trials included in the meta-analysis

Author	Year	Country	Number of patients	Mean age, years	Men, %	Study period	Kidney transplant type (deceased/living donor)	Time since transplantation	Generic immunosuppressant (manufacturer, country)	Mean dose	Concomitant immunosuppressive regimen
<i>Neoral</i> [®]											
Kim and Han [33]	1998	Korea	40	39	75	4 weeks	0/40	4 weeks	Neoplanta (Hanmi Pharma Co., Korea)	10 mg/kg/day	NR
Khatami et al. [32]	2013	Iran	221	39	61	1 year	111/168	NR	Iminoral (Arta Co., Iran)	3–7 mg/kg	Corticosteroids and mycophenolate mofetil
Vitko and Ferkl [35]	2010	Czech Republic, Poland, Romania	99	42	70	6 months	NR	3.9 years	Equoral [®] (IVAX Pharmaceuticals, Inc., USA)*	2–6 mg/kg	Corticosteroids and mycophenolate mofetil or azathioprine
Ong et al. [34]	2007	Malaysia	106	41	54	6 months	68/38	4.3 years	Gengraf [®] (Abbott Laboratories, USA)*	150 mg	NR
<i>CellCept</i> [®]											
Abdallah et al. [15]	2010	Tunisia	18	35	61	2 years	4/14	NR	MMF 500 (Medis Laboratories, Tunisia)	2,000 mg	Prednisolone and tacrolimus
<i>Prograf</i> [®]											
Min et al. [36]	2013	Korea	117	46	59	10 days	63/54	NR	Tacrobell [®] (Chong Kun Dang, Seoul, Korea)	NR	Prednisone, and mycophenolate mofetil
NR = Not reported.											
* Approved by the FDA for use in the United States.											

Microoral[®], Arpimune-ME, Zaven-ME, Deximune[®], and Cicloral[®]. Two trials did not report the trade name of the generic drug [28, 31]. Most trials used a single-drug dose with 2 phases separated by 7 or 14 days, comprising >5 therapeutic half-lives.

In parallel-arm trials, Neoral[®] was compared to generic Neoplanta, Gengraf[®], Equoral[®] or Iminoral [32–35]. Trials varied in sample size (13–221 patients) and duration of follow-up (1–24 months).

The relative bioavailability of generic MMF was studied in 5 single-dose cross-over trials [16, 18, 21, 26, 27]. CellCept[®] was compared to generic MMF500TM, LinfonexTM or Suprimum 500[®]. Two trials did not report the trade name of the generic drug [16, 26]. The trials used a single-dose with 2 periods separated by a washout period ranging from 8 days to 7 weeks. One 2-year parallel-arm trial of 18 kidney transplant recipients compared CellCept[®] to MMF500TM [15].

Two single-dose cross-over trials (one trial with 2 sub-studies) examined the relative bioavailability of generic tacrolimus in healthy volunteers [22, 25]. Prograf[®] was compared to Tacrobell[®] and an unspecified generic for-

mulation. One parallel-arm trial of 117 kidney transplant recipients of 10-day duration compared Prograf[®] to Tacrobell[®] [36].

Risk of Bias Assessment

While all trials exhibited a lower risk of selection bias (random sequence generation and allocation concealment), there was a higher risk of performance bias (lack of blinding of participants and personnel), detection bias (blinding of outcome assessment), and reporting bias (selective reporting) (online suppl. efig. 1–3).

Pooled Analyses of Generic Cyclosporine Bioavailability Studies in Healthy Volunteers

Eleven single-dose cross-over trials of healthy volunteers examined the relative bioavailability of generic cyclosporine formulations to Neoral[®] [17, 19, 20, 23, 24, 28, 30, 31, 37]. Although the pooled peak plasma concentration of generic cyclosporine formulations, as measured by the C_{max} , was significantly lower than that achieved by Neoral[®], the FDA requirement for bioequivalence was met (pooled C_{max} T/R ratio 0.91; 90% CI 0.86–0.95; $p =$

Fig. 2. Forest plot displaying the pooled weighted ratio of the T/R immunosuppressive drug for the mean C_{max} with the corresponding 90% CI. ‘Test’ refers to the generic immunosuppressive drug, and ‘reference’ to its brand counterpart.

0.001; fig. 2). However, there was significant heterogeneity ($I^2 = 74.9\%$; $p < 0.001$), with inclusion of study participants of diverse geographic and ethnic background.

The pooled extent of absorption of generic cyclosporine, expressed as $AUC_{(0-t)}$, was also significantly lower than that achieved by Neoral®, but the FDA requirement for bioequivalence was also met (pooled $AUC_{(0-t)}$ T/R ratio 0.97; 90% CI 0.94–1.00; $p = 0.001$; fig. 3). There was no evidence of heterogeneity. Of note, however, in one study from India, the 90% CI of the $AUC_{(0-t)}$ T/R ratio exceeded the 0.8–1.25 range ($AUC_{(0-t)}$ T/R ratio 1.09; 90% CI 0.93–1.29), raising concerns about its potential safety in the studied population [28].

One trial adopted a different design testing multiple cyclosporine dosages and included dialysis patients awaiting kidney transplantation [29]. In a sensitivity analysis that included this study, the pooled C_{max} and $AUC_{(0-t)}$ T/R ratio and respective 90% CI met the FDA requirement for bioequivalence (pooled C_{max} T/R ratio 0.91; 90% CI 0.87–0.96; and pooled $AUC_{(0-t)}$ T/R ratio 0.97; 90% CI 0.94–0.99).

There was no significant difference between generic cyclosporine formulations and Neoral® with respect to T_{max} (pooled WMD -0.05 ; 95% CI -0.17 to 0.08 ; fig. 4) [17, 19, 20, 23, 24, 28, 30, 31, 37] and $T_{1/2}$ (pooled WMD 0.03 ; 95% CI -0.07 to 0.13 ; fig. 5) [17, 19, 20, 23, 24, 28, 31, 37].

Pooled Analyses of Generic Tacrolimus Bioavailability Studies in Healthy Volunteers

Three single-dose cross-over trials (2 citations) examined the relative bioavailability of generic tacrolimus formulations to Prograf® [22, 25]. Although the pooled C_{max} of generic tacrolimus formulations was significantly higher than that achieved by Prograf®, the FDA requirement for bioequivalence was met (pooled C_{max} T/R ratio 1.17; 90% CI 1.09–1.24; $p = 0.01$; fig. 2). The pooled $AUC_{(0-t)}$ also met the FDA requirement for bioequivalence (pooled $AUC_{(0-t)}$ T/R ratio 1.00; 90% CI 0.97–1.03; $p = 0.01$; fig. 3). In one trial from Korea [25], the C_{max} of Tacrobell® was greater than that achieved for Prograf®, raising concerns

Fig. 3. Forest plot displaying the pooled weighted ratio of the T/R immunosuppressive drug for the mean AUC_(0-t), with the corresponding 90% CI. ‘Test’ refers to the generic immunosuppressive drug, and ‘reference’ to its brand counterpart.

Fig. 4. Forest plot displaying the pooled weighted mean difference of the brand versus generic immunosuppressive drug for the mean T_{max}, with the corresponding 95% CI. ‘Test’ refers to the generic immunosuppressive drug, and ‘reference’ to its brand counterpart.

Fig. 5. Forest plot displaying the pooled weighted mean difference of the brand versus generic immunosuppressive drug for the mean $T_{1/2}$, with the corresponding 95% CI. “Test” refers to the generic immunosuppressive drug, and “reference” to its brand counterpart.

about the safety of this generic formulation. There was no significant difference between generic tacrolimus formulations and Prograf® with respect to $T_{1/2}$ (pooled WMD -0.27; 95% CI -2.00 to 1.47; $p = 0.76$; fig. 5) [22, 25].

Pooled Analyses of MMF Bioequivalence Studies in Healthy Volunteers

Five trials examined the relative bioavailability of generic MMF formulations to CellCept® [16, 18, 21, 26, 27]. Although the pooled C_{max} of MMF generic formulations was significantly lower than that achieved by CellCept®, the FDA requirement for bioequivalence was met (pooled C_{max} T/R ratio 0.98; 90% CI 0.96–1.01; $p = 0.001$; fig. 2). The pooled $AUC_{(0-t)}$ also met the FDA requirement for bioequivalence (pooled $AUC_{(0-t)}$ T/R ratio 1.00; 90% CI 0.99–1.01; $p = 0.001$; fig. 3). No heterogeneity was detected. There was no significant difference between generic MMF formulations and CellCept® with respect to T_{max}

(pooled WMD -0.10; 95% CI -0.51 to 0.31; $p = 0.98$; fig. 4) [18, 26, 27] and $T_{1/2}$ (pooled WMD 0.39; 95% CI -0.35 to 1.14; $p = 0.30$; fig. 5) [16, 26].

Pooled Analyses of Efficacy and Safety Studies in Kidney Transplant Recipients

Four parallel-arm trials, totaling 466 kidney transplant recipients, compared generic cyclosporine formulations to Neoral® [32–35]. All 4 trials reported on kidney allograft rejection [32–35], 2 trials on AEs and SAEs [34, 35], 3 trials on infections [32, 34, 35], and 3 trials on mortality [32, 34, 35]. Generic cyclosporine formulations appeared non-inferior to Neoral® with respect to acute allograft rejection (pooled OR 0.95; 95% CI 0.46–1.93), infections (pooled OR 0.91; 95% CI 0.52–1.60), AEs (pooled OR 1.01; 95% CI 0.55–1.85), SAEs (pooled OR 1.80; 95% CI 0.82–3.91), and death (pooled OR 2.77; 95% CI 0.39–19.75).

The evidence on efficacy and safety of MMF and tacrolimus was limited. One trial of 18 incident kidney transplant recipients observed a higher rate of acute kidney injury in patients receiving the reference drug CellCept® (66.6 vs. 14.3%); however, the 2 groups had comparable rates of acute allograft rejection (14.3 vs. 16.6%) [15]. In the single trial of 126 incident kidney transplant recipients examining the efficacy and safety of a generic tacrolimus formulation (Tacrobell®), there were no significant differences in the incidence or severity of patient-reported AEs between the 2 groups [36]. However, subclinical acute allograft rejection rates were more frequently observed in patients receiving generic tacrolimus compared to Prograf® (14.8 vs. 3.2%, $p = 0.04$).

Investigations of Heterogeneity

Subgroup analyses comparing the brand drug with each generic formulation could only be performed for cyclosporine, and with 2 generic formulations, Cicloral® and Sigmasporin Microral®. In the 4 crossover trials and sub-studies, comparing Cicloral® to Neoral® [19, 20], Cicloral® did not meet the FDA criteria for bioequivalence with respect to the $C_{\max}$ (pooled $C_{\max}$ T/R ratio 0.82; 90% CI 0.78–0.86; $p = 0.001$; online suppl. efig. 4). Data on $AUC_{(0-t)}$ were not available. There was no significant difference between Cicloral® and Neoral® with respect to $T_{\max}$ (pooled WMD -0.05 ; 95% CI -0.17 to 0.08 ; online suppl. efig. 6) and $T_{1/2}$ (pooled WMD -0.05 ; 95% CI -0.36 to 0.25 ; online suppl. efig. 7).

In the 3 crossover trials comparing Sigmasporin Microral® to Neoral® [23, 24, 30], Sigmasporin Microral® met the FDA criteria for bioequivalence in terms of $C_{\max}$ (pooled $C_{\max}$ T/R ratio 0.96; 90% CI 0.90–1.02; online suppl. efig. 4) and $AUC_{(0-t)}$ (pooled T/R ratio 0.95; 90% CI 0.89–1.02; $p = 0.94$; online suppl. efig. 5), but there was no significant difference with respect to $T_{\max}$ (pooled WMD -0.13 ; 95% CI -0.44 to 0.18 ; online suppl. efig. 6) and $T_{1/2}$ (pooled WMD -0.24 ; 95% CI -0.82 to 0.33 ; online suppl. efig. 7).

Discussion

In the present systematic review, we summarize the existing literature on the bioavailability of generic immunosuppressive drugs relative to their brand counterparts in healthy subjects, and their efficacy and safety in kidney transplant recipients. Most of the included reports focused on cyclosporine, followed by tacrolimus and MMF. None of the immunosuppressive drugs identified in this

synthesis are currently approved for use in the United States except for 2 generic formulations of cyclosporine, Equoral® and Gengraf®. To examine relative bioavailability, however, we followed the FDA guidance by comparing the rate ($C_{\max}$) and extent ($AUC_{(0-t)}$) of absorption of generic formulations available worldwide relative to their brand counterparts. We also examined the efficacy and safety of generic cyclosporine formulations relative to the brand cyclosporine Neoral®. Limited data precluded similar analyses for tacrolimus and MMF. Generic formulations of cyclosporine, tacrolimus, and MMF met the FDA requirement for bioequivalence against their respective brand counterparts on the basis of the 90% CI of 0.80–1.25 for the T/R drug's $C_{\max}$ and $AUC_{(0-t)}$. However, substantial heterogeneity was observed. In subgroup analyses, the $C_{\max}$ achieved by Cicloral® relative to Neoral® did not meet the FDA criteria for bioequivalence, raising concerns about its pharmacokinetic profile. In terms of efficacy and safety, generic cyclosporine formulations appeared non-inferior to Neoral® in kidney transplant recipients; however, the results were deemed inconclusive due to the wide confidence limits around the effect estimates.

Although cheaper than their brand counterparts, there is controversy as to whether reduced cost of generic immunosuppressive drugs translates into lower healthcare costs [38]. A study of incident kidney transplant recipients found that first-year costs were significantly higher in patients receiving generic cyclosporine, compared to those treated with brand cyclosporine, due to dose escalation or addition of another immunosuppressant [7]. Based on the variable absorption profile of generic drugs in certain populations, we can only speculate as to whether certain characteristics such as ethnicity must be considered when choosing a generic drug, and policies might be required to better specify the target population where the generic drug could safely be used according to results of bioequivalence studies.

Controversy regarding the use of generic immunosuppressive drugs has impacted patients' perceptions. Clinical equivalency of generic medications is accepted by 75% of patients maintained on generic substitutes and only 54% by those maintained on brand drugs [39]. However, a survey of kidney transplant recipients found that 75% did not know whether they were taking generic substitutes, yet 84% felt that generic substitutes were not consistently equivalent to their brand counterparts [40].

Among the multiple potential factors that can impact outcomes in patients receiving immunosuppressants, pharmaceutical inter- and intra-batch heterogeneity is a

major safety and efficacy concern for drugs with a narrow therapeutic index. Although generic substitutes in the United States currently comply with the 90% CI range of 80–125% to satisfy bioequivalence for $C_{\max}$ and $AUC_{(0-t)}$, intra-patient variability in serum trough levels of generic immunosuppressive drugs has been observed in kidney transplant recipients with impact on allograft related outcomes [41, 42]. Canada and Europe have implemented policies to reduce pharmaceutical heterogeneity of drugs with a narrow therapeutic index by narrowing the 90% CI range of the $AUC_{(0-t)}$ for generic drug approval to 90–111%.

Our results are in agreement with a recently published meta-analysis that included randomized controlled trials and observational studies [43]. The authors examined bioequivalence of generic to brand immunosuppressive drugs by comparing 2 pharmacokinetic parameters, the $AUC_{(0-t)}$ and $C_{\max}$. There were only 2 trials (a parallel arm and a cross-over trial) of MMF to allow for a pooled analysis. Cross-over and parallel-arm trials were also combined, and one trial had a questionable randomization procedure [44].

Strengths of our synthesis include a comprehensive literature search and rigorous analytical methods. For the study of bioequivalence, we included only crossover trials deemed compliant with the FDA guidelines. The trials enrolled healthy subjects from several countries and of variable ethnicity. For several pharmacokinetic parameters, there was no significant heterogeneity, justifying the aggregation of the data. An important limitation is the relatively small number of trials, and the inability to extrapolate data derived from healthy volunteers to kidney transplant recipients. Chronic kidney disease is associated with altered intestinal transport mechanisms, which can affect the oral bioavailability of immunosuppressive drugs [45], and increase the risk for adverse reactions [46]. Furthermore, we included studies of populations from different regions of the world, including Europe, Africa, and the Middle East. This variability likely contributed to the heterogeneity in the bioavailability study results, as drug absorption and metabolism is affected by race, ethnicity and genetic factors. Finally, there were very few parallel-arm trials of efficacy and safety, and cyclosporine was the only drug where results could be pooled.

In conclusion, the use of generic immunosuppressive drugs for kidney transplantation remains a debatable issue with varying views regarding their bioequivalence, efficacy, and safety. The evidence surrounding the bioequivalence of generic cyclosporine, tacrolimus, and

MMF indicate that their generic counterparts with the exception of Cicloral® appear to have similar bioavailability in healthy volunteers. However, none of the generic drugs tested in these bioavailability studies is currently approved for use in the United States. While the efficacy and safety of generic cyclosporine in kidney transplant recipients suggest non-inferiority to its brand counterpart, the evidence is inconclusive and this drug has become less relevant in the modern era of organ transplantation, with 92% of kidney transplant recipients now being prescribed tacrolimus as the first-line calcineurin inhibitor [47]. Practicing clinicians should be aware of the variable rate and extent of absorption that generic immunosuppressive drugs might display, and as a result, monitor serum drug levels frequently, and be alert of potential AEs that might occur due to differences in absorption rates. Moreover, adoption of stricter regulatory guidelines for approving generic drugs with a narrow therapeutic index might increase their efficacy and safety.

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Disclosure Statement

The authors declare that they have no other relevant financial interests.

Contributions

Dr. B.L. Jaber had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: E. Tsiptotis, B.L. Jaber. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: E. Tsiptotis, N.R. Gupta, B.L. Jaber. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: G. Raman, E. Zintzaras. Obtained funding: not applicable. Administrative, technical, or material support: E. Tsiptotis, N.R. Gupta. Study supervision: B.L. Jaber.

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