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Generic immunosuppression in solid organ transplantation: a systematic review and meta-analysis

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The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Abstract

Objective: To compare the clinical efficacy and bioequivalence of generic immunosuppressive medications in the solid organ transplant population.

Design: Systematic review and meta-analysis of all studies comparing generic with brand name immunosuppressive medications.

Data sources: MEDLINE and EMBASE from 1980 to September 2014.

Review methods: A literature search was performed for all studies comparing a generic to a brand name immunosuppressive drug in solid organ transplantation. Two reviewers independently extracted data and assessed quality of studies. Meta-analyses of pre-specified outcomes were performed when deemed appropriate. Outcomes included patient survival, allograft survival, acute rejection, adverse events and bioequivalence.

Results: 1,679 citations were screened of which n=50 studies met eligibility criteria (17 randomized trials, 15 non-randomized interventional studies and 18 observational studies). Generics were compared to Neoral (cyclosporine) (n=32 studies), Prograf (tacrolimus) (n=12 studies) and Cellcept (mycophenolate mofetil) (n=6 studies). 11 studies met established criteria for bioequivalence (Neoral n=10, Prograf n=1 and Cellcept n=0). Acute rejection was rare but did not differ between groups (Neoral pooled Peto OR (95% CI) for kidney RCT's and observational studies 0.81 (0.42 to 1.57), 0.66 (0.40 to 1.08), respectively; Prograf pooled Peto OR (95% CI) for kidney observational studies 0.98 (0.37 to 2.60); Cellcept pooled Peto OR for kidney observational studies 0.49 (0.09 to 2.56)). There was insufficient data reported on patient or graft survival.

Limitations: Pooling of results was limited by inconsistent study methodology and reporting of outcomes. Many studies did not report standard criteria used to determine

bioequivalence. While acute rejection rates appeared similar and were relatively rare, few studies were designed to properly compare clinical outcomes. The majority of studies had short follow up times and included stable patients without a history of rejection.

Conclusions: There is limited and inconsistent data on the bioequivalence and clinical efficacy of generic immunosuppressive medications in the transplant population. Given the serious consequences of rejection and allograft failure, well-designed studies are needed to demonstrate the safety and efficacy of generic immunosuppression.

What this paper adds

There are an increasing number of generic immunosuppresants available for use in the solid organ transplant population. These generics are approved after meeting the current standards for bioequivalence with the brand name reference drug. Given the potential for organ rejection if a generic immunosuppressant is not equivalent, there is growing concern that the current criteria for approval are not rigorous enough. Our systematic review and meta-analysis found a lack of high quality data supporting the equivalence of generics and brand name immunusoppressants but also a lack of data to suggest that they are not equivalent. High quality studies on this issue are needed.

INTRODUCTION

With the recent patent expiry of commonly prescribed immunosuppressive medications such as Prograf (tacrolimus) and Cellcept (mycophenolate mofetil), the use of generics in solid organ transplantation has become controversial.[1-5] Generic substitution has the potential for huge cost savings.[1] However, there is significant concern among physicians and patients that generics are not equivalent to the brand name versions of immunosuppressant drugs.[6-9]

Prior to approval, each generic drug must demonstrate bioequivalence to the brand name version in healthy adults, but there is no requirement to show bioequivalence or clinical efficacy in transplant patients. Many argue that the current criteria are not sufficient as transplant patients often have co-morbidities and are on multiple medications, which could alter the pharmacokinetics of a drug.[1,3,4] Also, bioequivalence may not necessarily mean equivalence in terms of clinical effectiveness, which could lead to catastrophic consequences in a transplant patient (i.e., loss of the graft). However, based on current guidelines, clinical effectiveness is assumed if bioequivalence can be demonstrated.[10] The concerns raised in the transplant community have led to the recommendation that patients and healthcare providers pay careful attention to drug formulations, and monitor drug levels more frequently if a patient is switched to a generic preparation.[2,4,11] Certain countries in Europe, such as the United Kingdom and Denmark, have gone even further and banned the generic substitution of tacrolimus and cyclosporine products.[12,13] These recommendations are not based on high quality evidence, and many, including regulatory agencies, argue that the methods of determining bioequivalence are reliable and

sufficient.[14,15] If patients and physicians remain doubtful of the equivalence of generic immunosuppressive medications, this will limit the cost saving potential of these medications due to under-prescribing and more frequent laboratory monitoring when a generic is prescribed.[1,16] The aim of this study was to determine the clinical efficacy, safety and bioequivalence of generic immunosuppressive medications compared to brand name formulations in solid organ transplant recipients. Our focus was on clinically important outcomes, such as patient survival, transplant allograft survival and acute rejection.

METHODS

Search strategy

We performed a comprehensive, systematic search of articles published in peer-reviewed journals using MEDLINE and EMBASE (1980 to September 4th, 2014). The search was carried out with the assistance of a librarian experienced in systematic reviews. A structured search strategy, (outlined in Appendix A), was conducted using controlled vocabulary and relevant key terms to enhance sensitivity. Reference lists of included papers and previous reviews were hand-searched for additional relevant studies. There were no restrictions based on study design or language in the search.

Study Selection

An initial screen of identified titles and abstracts was performed by one investigator (AM). Titles and abstracts deemed to be clearly irrelevant were removed on the initial screen. A second screen to identify potentially relevant studies was performed by two independent reviewers (AM and AT). If no abstract was available, the full text was

obtained unless the article could be confidently excluded by title alone. If there was any doubt as to whether or not a study could be excluded, a full text screen was performed to reduce the likelihood of incorrectly excluding a relevant study. Full-text versions of potentially eligible studies were obtained and independently screened by two reviewers (AM and AB) to determine their eligibility based on the selection criteria. Any disagreements during the screening process were resolved through discussion amongst the authors in accordance with the selection criteria.

Randomized controlled trials (RCT), non-randomized interventional studies and observational studies were included if they reported a comparative evaluation of a brand name immunosuppressive medication to at least one generic version of the same drug in solid organ (heart, lung, liver, pancreas, kidney, small bowel or combinations of these organs) transplant recipients. The comparative evaluation had to include at least one clinical efficacy/safety outcome, [death, transplant failure, acute rejection, marker of graft function (e.g. serum creatinine), health care utilization (e.g. hospitalization), infection, drug concentration or other serious adverse event], or the determination of bioequivalence. There are different definitions of bioequivalence depending on the jurisdiction. In the United States, the Food and Drug Administration (FDA) requires that the 90% confidence interval of the mean ratio (generic/brand) for the area under the curve (AUC) of the concentration-time curve and the peak concentration (C_{max}) be between 80% and 125%.[10,17-19] For narrow therapeutic index drugs (e.g. cyclosporine and tacrolimus), Health Canada (HC) and the European Medicines Agency (EMA) have tighter limits for the AUC acceptance interval (90% to 112% and 90% to 111%,

respectively).[10,20] For cyclosporine, the EMA has also imposed tighter limits for the Cmax acceptance interval (90% to 111%).[20] In this analysis, bioequivalence was assessed using both the FDA definition and the tighter standards from the EMA and Health Canada. Comparative studies that evaluated Sandimmune were excluded since this formulation is no longer used in clinical practice. We also excluded case reports, case series, studies including pediatric patients and studies performed on animals or conducted in vitro.

Data extraction and synthesis

Three investigators (AM, AD, NF) abstracted data. Each eligible study had data independently abstracted by two different investigators (see Appendix B for data abstraction form). A number of variables related to the organization and outcome of the studies were assessed: study design, setting (country), characteristics of the population studied, transplant organ, number of study participants, immunosuppressive medication studied, and reporting of relevant outcomes. The primary clinical efficacy outcome was acute rejection and the primary bioequivalence outcome was the mean ratio (and 90% confidence interval) for the C_{max} and AUC. The methodological quality of eligible randomized trials (parallel and cross over designs) was evaluated using the Cochrane Risk of Bias Assessment Tool.[21] The methodological quality of observational and non-randomized experimental studies was evaluated using a checklist outlined by Wells *et al*.[22] Quality assessment was performed for studies as a whole and separately for each pre-specified primary outcome. When data was only available in figures, the GNU image manipulation program (GIMP 2.8; http://www.gimp.org/) was used to extract data.

Statistical analysis

Descriptive methods were used to present the data by type of immunosuppressive medication, type of organ transplant and outcome. For the randomized trials and non-randomized interventional studies, we pooled the mean ratio and the 90% confidence interval for the C_{max} and AUC. Data was analyzed using the inverse variance method with a random effects model and presented as a pooled mean ratio with a 90% confidence interval. The standard errors of the AUC and C_{max} mean ratios were calculated using the 90% or 95% confidence intervals and T statistic of the study. Continuous efficacy outcomes, (e.g. serum creatinine), were pooled when deemed appropriate using the inverse variance method and presented as weighted mean differences. Dichotomous efficacy outcomes, (e.g. acute rejection), were pooled using the Peto method and presented as the Peto odds ratio (OR). The Peto OR was selected as it is the preferred estimate when cells contain 0 events. Cross-over trials were treated as parallel group trials in the analysis if individual patient-level data, sequence specific data or correlation coefficients were not available.[23] A pre-specified sensitivity analysis was performed for cyclosporine that excluded studies involving SangCya since it was recalled in 2000 and is no longer available.[24] Heterogeneity was assessed using the I^2 statistic. Meta-analyses were performed using RevMan 5.3. Data from observational studies were not pooled for the outcome of bioequivalence due to concerns about the validity of the results. Data from cross over trials and before/after studies were not pooled for the outcome of acute rejection due to concerns about the statistical and clinical validity of the results. The reporting of this systematic review is in accordance with PRISMA guidelines (refer to Appendix B for details).[25]

RESULTS

Eligible studies

The electronic database search identified 2,558 records and 6 further records were identified from reference lists. After independently reviewing the title and abstract of all potentially relevant records, 201 articles were retrieved and reviewed in full text. Of these, 50 studies were found to meet inclusion criteria. Study selection is outlined in Figure 1.

Patient and study characteristics

The characteristics of the 50 eligible studies are outlined in Supplementary Tables 1 a, b and c. Eligible studies included kidney, heart and liver transplant recipients. Study designs included RCTs (n=17; 8 cross-over and 9 parallel), non-randomized interventional studies (n=15) and observational studies (n=18; cohort and before/after designs). Brand name drugs studied included Neoral (cyclosporine; n= 32 studies[26-57], 28 in kidney transplants, 3 in heart transplants, and 1 in liver transplants), Prograf (tacrolimus; n= 12 studies[58-69], 7 in kidney transplants, 1 in heart transplants, 1 in liver transplants, and 3 in a mixture of liver, kidney or heart transplants) and Cellcept (mycophenolate mofetil; n= 6 studies[70-75], 5 in kidney transplants and 1 in liver transplants). Neoral was compared to 12 different generic medications (Iminoral, Equoral, Gengraf, Cysporin, Zinograf-ME, Neoplanta, Consupren, SangCya (Sang-35), Sigmasporin Microral, Pliva, Cicloral, and Arpimune); Prograf was compared to four different generics (Tacni, Tacrobell, Adoport, and Sandoz-tacrolimus); and Cellcept was compared to five different generics (Myfenax, Medis, Linfonex, Mycept, and Myconol).

Neoral studies

Sample sizes ranged from 11 to 221 patients although one study did not report the number of included patients.[38] The average age in most studies was 40-50 years. Eight studies included incident transplants.[34,35,40,45-48,57] (Supplementary Table 1a)

Prograf studies

Sample sizes ranged from 25 to 234 patients. The average age in most studies was between 50-60 years of age, except for the Robertsen *et al.* study that included only patients 60 years or older.[69] Five studies included incident transplant.[59,60,63,66,69] (Supplementary Table 1b)

Cellcept studies

The sample sizes ranged from 5 to 56 patients. Three studies included incident transplant recipients.[70,72,74] (Supplementary Table 1c)

Assessment of study quality

Randomized trials

The methodological quality of the RCTs was generally poor (Supplementary Fig 1). Only four RCTs reported on the methods used for randomization,[29,57,63,69] and allocation concealment was poorly reported. There were only two double-blind trials[54,69], one of which was a RCT that had concerns about selective reporting of outcomes.[54]

Non-Randomized Interventional Studies and Observational Studies

The quality assessment of the non-randomized studies is presented in Supplementary Table 2. All non-randomized interventional studies had a before/after design, with patients serving as their own control. Observational studies were a mixture of retrospective and prospective designs. Most cohort studies identified patients as receiving generic or brand name medication based on era (e.g. the brand name was used in 2007 and the generic in 2008). Many studies did not account for potential confounders, such as dose adjustments, in their analyses.

Outcomes

Pharmacokinetic and clinical outcomes are summarized in Supplementary Tables 3 and 4, respectively. Where applicable, most studies explicitly stated that there was a mg:mg conversion from brand name to generic, however some studies allowed dose adjustments following the initial conversion while others did not clearly state whether or not dose adjustments were allowed.

Neoral

Ten studies (n=9 kidney transplant; n=1 liver transplant) reported 90% confidence intervals for the primary pharmacokinetic outcomes of the Cmax and AUC mean ratios.[27,32,33,39,41,43,51,53-55] All reported 90% CI's for the Cmax and AUC mean ratios fell within the FDA guidelines for bioequivalence. However, seven studies reported 90% CI's for the Cmax and AUC mean ratios that did not meet the stricter EMA bioequivalence criteria,[27,32,33,51,53-55], and five studies did not meet the Health Canada bioequivalence criteria, based on the 90% CI of the AUC mean ratio.[33,51,53-55] When results were pooled

for the randomized kidney trials (n=2)[33,53], the FDA criteria for bioequivalence were met while the EMA/Health Canada guidelines were not met. Pooling of the results for non-randomized interventional kidney studies[25,30,39,41,47,49,55] met FDA/EMA/Health Canada bioequivalence criteria (Table 1a). There was variable reporting of other secondary pharmacokinetic outcomes (Supplementary Table 3a).

For clinical outcomes, follow up ranged from 1 week to 1 year. Acute rejection was reported in 16 studies, 8 of which reported no episodes of acute rejection[36,37,43,44,50-52], while one study had a large number of acute rejections (n=59).[46] Two studies reported a significant increase in acute rejection for those receiving generics compared to Neoral (39% vs. 25%, P=0.04[46] and 60% vs. 25%, P<0.05[44]). Acute rejection was pooled for the randomized parallel group kidney trials that measured the outcome at 6 months or greater.[47,52,57] No significant difference in acute rejection was found (pooled Peto OR 0.81; 95% CI 0.42 to 1.57) (Figure 2a). No significant difference in acute rejection was found when results from observational kidney studies were pooled (pooled Peto OR 0.66; 95% CI 0.40 to 1.08) (Figure 2b). There were 8 studies that reported graft loss and 9 that reported patient survival. Of the studies that reported graft loss, only 2 episodes occurred, and these were in the Neoral arm[45,57] (Supplementary Table 4a). Serum creatinine data was pooled for the randomized parallel group kidney trials that measured creatinine at 6 months or greater.[47,56,57] Serum creatinine was not significantly different between the Neoral and generic arms (mean difference 6.45 umol/L; 95% CI -0.67 to 13.57) (Supplementary Figure 2).

Prograf studies

Three kidney RCTs reported the primary pharmacokinetic outcome of the C_{max} and AUC.[58,63,69] When data was pooled, the 90% CI's for the AUC and C_{max} mean ratios did not meet FDA, EMA or Health Canada bioequivalence criteria (Table 1b). When each study was examined individually, two studies did not meet FDA, EMA or Health Canada bioequivalence criteria[63,69] (Supplementary Table 3b).

For clinical outcomes, follow up ranged from 4 weeks to 1 year, with only 1 study having a follow up beyond 6 months. Of the studies that reported the outcome of acute rejection (n=10 studies), five reported no events. The only study that reported a difference (not statistically significant) in the incidence of acute rejection was by Yu *et al.,* (8% vs. 0% in the Prograf and generic arms respectively, p=0.08).[66] Acute rejection was pooled for the observational kidney studies that measured the outcome at 6 months or greater.[59,61,62] No significant difference in rejection was found (Peto OR 0.98; 95% CI 0.37 to 2.60) (Figure 3). The study with the most acute rejection, (8 in the Prograf arm and 9 in the generic arm), was also the only study that reported patients with graft loss (6 in the Prograf arm and 8 in the generic arm, p=0.776).[59] The outcome of serum creatinine was measured at different time points in each study and therefore could not be pooled. There was no significant difference in serum creatinine between Prograf or generic arms in any of the studies that reported the outcome (Supplementary Table 4b).

Cellcept studies

One study (cross over trial in kidney transplants) reported the AUC (0.899 to 1.023) and C_{max} (0.787 to 0.968) 90% CIs.[73] These values did not fulfill the FDA/EMA or Health Canada requirements for bioequivalence (Supplementary Table 3c).

For clinical outcomes, follow up ranged from 3 months to 2 years. One RCT reported acute rejection and there was only one event in each arm.[70] Acute rejection was pooled for the observational kidney studies that measured the outcome at 6 months or greater. No significant difference in rejection was found (Peto OR 0.49; 95% CI 0.09 to 2.56) (Figure 4). One study reported graft loss but there were no events[74] (Supplementary Table 4c).

Sensitivity Analysis

The Neoral bioequivalence meta-analysis was repeated after removing studies that used Sang-Cya[53,55], which did not significantly change the results.

DISCUSSION

Principal findings

This analysis included 50 studies comparing generic to brand name immunosuppression in greater than 3,130 solid organ transplant recipients. We found that generic cyclosporine met FDA but not EMA or Health Canada criteria for bioequivalence. Neither generic tacrolimus nor mycophenolate mofetil met any agency's criteria for bioequivalence. There was no significant difference in acute rejection for generic cyclosporine, tacrolimus or mycophenolate mofetil compared to brand name products.

Other important clinical outcomes, such as patient and graft survival were inconsistently reported with very few events occurring. Importantly, methodological quality of most studies was poor limiting inferences that can be made from this data.

Only 10 of 32 cyclosporine studies, (one in liver transplants and 9 in kidney transplants), reported the standard criteria needed to determine bioequivalence, and the results were inconsistent. As well, the lone published study conducted in liver transplants examined the generic Sang Cya, which is no longer approved for use. Available data suggest that the cyclosporine generics studied are bioequivalent to Neoral based on FDA criteria when used in kidney transplants. It remains unclear if Neoral and generic cyclosporine are bioequivalent based on EMA and Health Canada criteria and if bioequivalence exists in non-kidney solid organ transplant recipients.

Only 3 of 12 tacrolimus studies reported bioequivalence criteria. All 3 studies were RCT's and conducted in kidney transplants. Only Alloway *et al*[58] found bioequivalence (according to FDA/EMA/Health Canada criteria), and pooling of study results did not demonstrate bioequivalence. Included patients differed between the 3 studies, which could potentially explain the inconsistent results. Another potential explanation is that each study compared a different generic preparation to Prograf. Only 1 of 6 mycophenolate mofetil studies reported bioequivalence criteria. This study was a RCT conducted in stable kidney transplants and did not show bioequivalence. Overall, it remains unclear if generic tacrolimus or mycophenolate mofetil are bioequivalent to

Prograf and Cellcept respectively, and there is a complete lack of data in non-kidney solid organ transplant recipients.

Acute rejection was found to be no different for all generics. For generic cyclosporine, only kidney transplant studies were included in the meta-analysis for acute rejection due to a lack of data for other solid organ transplants. Two cyclosporine kidney studies found a higher rate of acute rejection in the generic arm compared to the Neoral arm. However, these studies had overall high rates of acute rejection, only included incident transplants, were single centre and were retrospective with historical controls. For generic tacrolimus, a low number of events significantly limited the ability to pool data, and acute rejection could only be pooled for kidney observational studies. The confidence intervals for 2 of the 3 meta-analyzed tacrolimus studies were extremely wide due to a low number of events. Five tacrolimus studies reporting acute rejection included liver and/or heart transplant recipients, 4 of which reported no events while one study with incident liver transplants reported a greater number of events, (although not statistically significant), in the Prograf arm. This study was retrospective, with the Prograf arm composed of historical controls; era effect could therefore potentially explain the greater number of events in the Prograf arm. For generic mycophenolate mofetil, 3 kidney studies and 1 liver study reported acute rejection, with no differences being found. Due to limited data, only kidney observational studies were included in the meta-analysis. Once again, a small number of events resulted in wide confidence intervals. Overall, the data for acute rejection must be interpreted with caution given the low number of observed events and

largely observational nature of the data. As well, there is a paucity of data for non-kidney solid organ transplants.

Comparison with other studies

To our knowledge, our study is the first systematic review and meta-analysis published on this topic. The number of generic immunosuppressants available on the market continues to rise. As a result, the prescription and safety of generic immunosuppressants have become increasing topics of concern, leading to the publication of multiple narrative reviews and editorials.[1,3,5,14-16,76-78] Our findings of an overall lack of high quality data supporting the bioequivalence and clinical efficacy of generic immunosuppressants in solid organ transplantation agree with that of a recently published narrative review.[1] The results of our review do not refute the current general consensus in the literature that any generic substitution be performed with caution or only in low-risk patients and that increased drug monitoring be performed post substitution, with the recognition that none of these recommendations are based on high quality evidence.[1-3,5,11,16] Our results also do not refute concern that the current method of determining bioequivalence, whereby a single dose cross over trial is performed in healthy volunteers, may not be sufficient for immunosuppressants in the solid organ transplant population.[1]

Strengths and limitations

Our review is comprehensive with the inclusion of all types of comparative peer reviewed published studies for three of the most commonly used immunosuppressants, and all of our primary outcomes of interest were pre-specified. Unfortunately, the

conclusions of our review are limited for several reasons. Included studies had inconsistent reporting of outcomes, limiting our ability to pool results. Although included studies were designed to examine the equivalence of a brand name drug to a generic, only a minority reported the 90% confidence intervals for the AUC and Cmax mean ratios, which are the standard criteria needed to determine bioequivalence.[10,17-20] Many studies only reported drug levels, which are not sufficient to comment on the bioequivalence of two drug preparations and can actually be misleading. In a recent study by Robertsen *et al.* that examined the bioequivalence of Prograf to a generic version, the generic was not found to be bioequivalent based on AUC and Cmax mean ratio criteria, however trough drug levels were identical.[69] This highlights the need for formal pharmacokinetic studies when commenting on bioequivalence. Of the minority of studies that reported criteria for bioequivalence, the results were inconsistent and inconclusive potentially due to varying study methodology and sample sizes.

Acute rejection was measured at various time points across studies, the methods of determining acute rejection were inconsistent across studies (clinical judgment *vs.* biopsy proven), and the majority of meta-analyzed studies were observational, making the results potentially more prone to bias and confounding. Several studies that measured acute rejection were not included in the meta-analysis due to significant concerns about validity and clinical applicability of the data. Approximately one third of all studies included in this review were interventional before/after or conversion studies and approximately one half of included trials were crossover design. These study designs can be useful when examining pharmacokinetic outcomes, such as drug levels, but not very

informative for clinical outcomes, such as acute rejection. Cross over trials generally have a short follow up time and can have a carry over effect; before/after studies are subject to an era effect bias, which is also a concern with many of the published cohort studies due to the use of historical controls. Published interventional before/after studies all specified as inclusion criteria stable graft function and many also specified no recent episodes of acute rejection, which creates a selection bias. The inclusion of only stable patients in the majority of studies is likely a contributing factor to the low number of observed events.

Overall, the quality of studies and study reporting were poor. The gold standard for determining bioequivalence and for comparing clinical outcomes is a randomized cross over trial[10,17,20] and a randomized parallel group trial, respectively, which the majority of studies were not. Of the one third of studies that were randomized trials, most were open label with unclear methods of randomization and allocation concealment. Also, many studies either allowed dose adjustments to occur prior to measuring drug levels or did not clearly report the timing of drug level measurements in relation to any dose adjustments or if dose adjustments were allowed to occur. This is obviously a concern since a patient should receive the same dose of both brand name and generic when comparing any sort of pharmacokinetic outcome.

Conclusions

In conclusion, high quality data demonstrating bioequivalence and clinical efficacy of generic immunosuppressants in solid organ transplants are lacking. There is insufficient

evidence to provide reassurance that generics are equivalent to brand name immunosuppressants, but there is also no data to firmly suggest that generics are not equivalent and therefore unsafe. As generics are considered standard of care in many jurisdictions, simple pragmatic trials with waived consent or cluster designs could efficiently answer unresolved questions. Without high quality data, the controversial issue of generic immunosuppressant prescribing will never be resolved, and the potential huge cost savings of these medications, if they are in fact equivalent, will never be fully realized.

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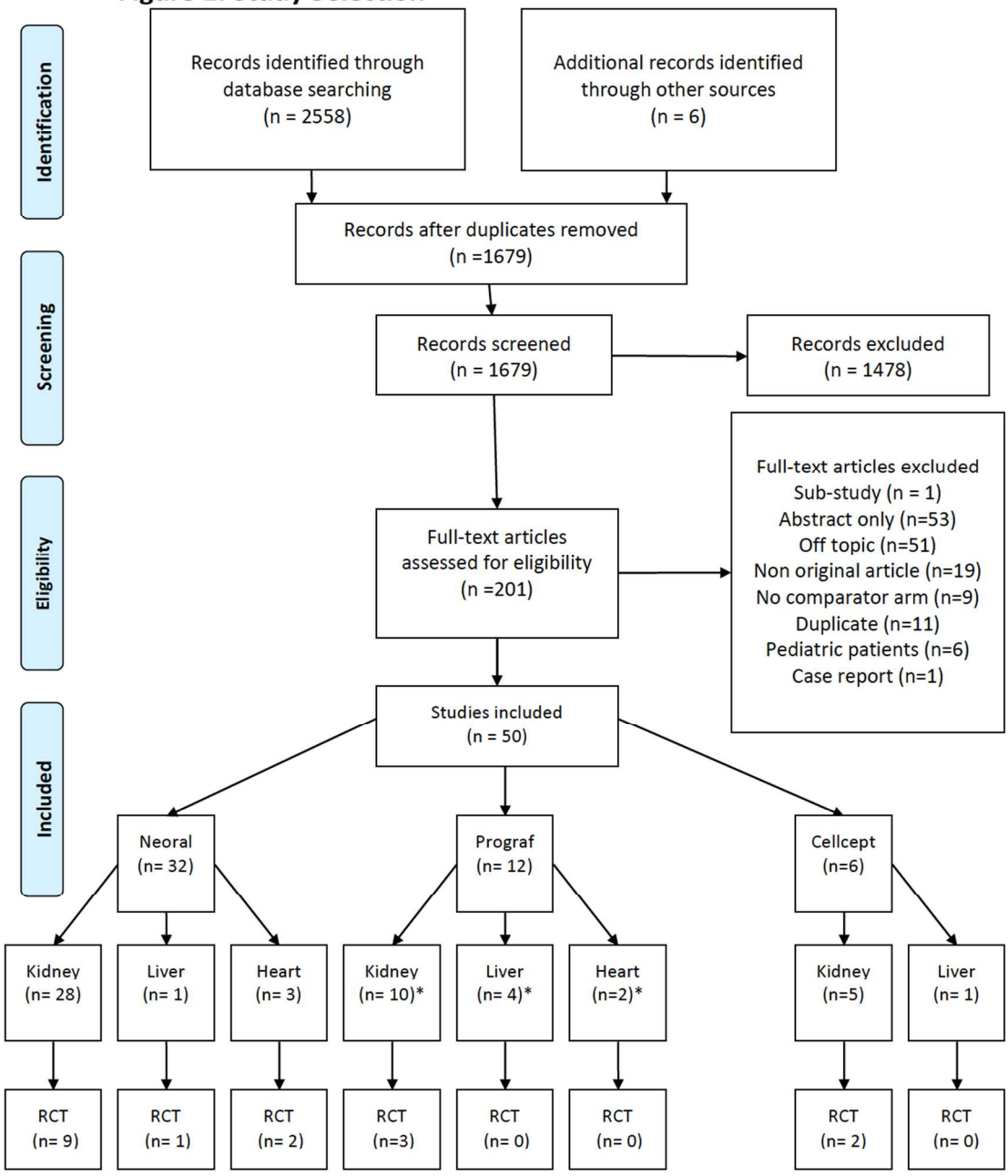
Figure 1: Study Selection



*Some studies included more than one type of transplant organ and were therefore counted more than once

Table 1a: Neoral meta-analysis of bioequivalence (Cmax and AUC mean ratios)

Neoral	No of Studies	No of patients	Point estimate (pooled 90% CI)	I^2 (%)	Meets FDA criteria	Meets EMA criteria	Meets HC criteria
AUC: kidney RCTs	2	60	0.93 (0.89 to 0.98)	0	Yes	No	No
AUC: non randomized interventional kidney studies	7	251	1.00 (0.98 to 1.02)	0	Yes	Yes	Yes
Cmax: kidney RCT's	2	60	0.90 (0.85 to 1.02)	0	Yes	No	Yes
Cmax: non randomized interventional kidney studies	7	251	0.98 (0.95 to 1.01)	0	Yes	Yes	Yes

Table 1b: Neoral meta-analysis of bioequivalence (Cmax and AUC mean ratios)

Prograf	No of Studies	No of patients	Point estimate (pooled 90% CI)	I^2 (%)	Meets FDA criteria	Meets EMA criteria	Meets HC criteria
AUC: kidney RCTs	3	222	1.09 (1.00 to 1.20)	76	Yes	No	No
Cmax: kidney RCT's	3	222	1.24 (1.02 to 1.50)	89	No	No	No

Cmax, maximum concentration
AUC, area under the curve
RCT, randomized controlled trial

Figure 2a: Neoral acute rejection kidney RCT's

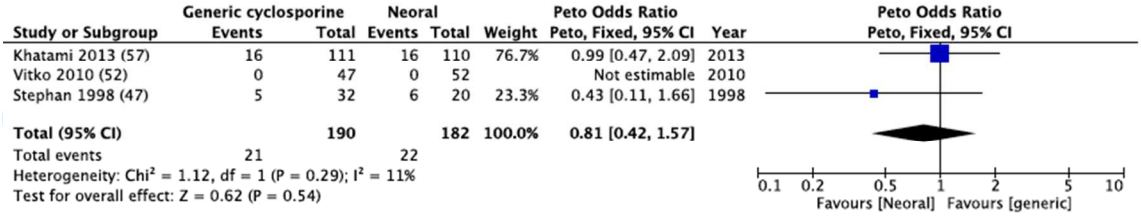


Figure 2b: Neoral acute rejection kidney observational studies

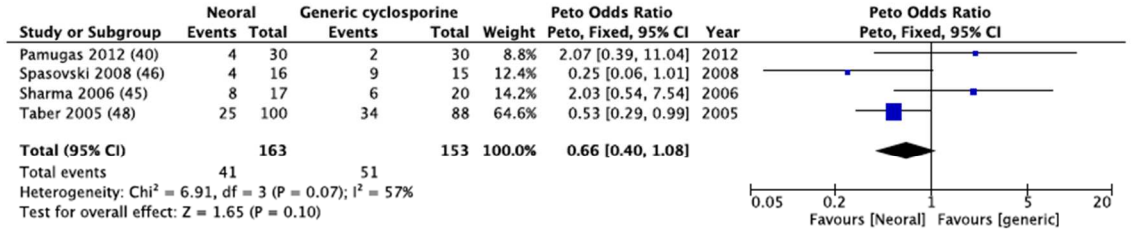


Figure 3: Prograf acute rejection kidney observational studies

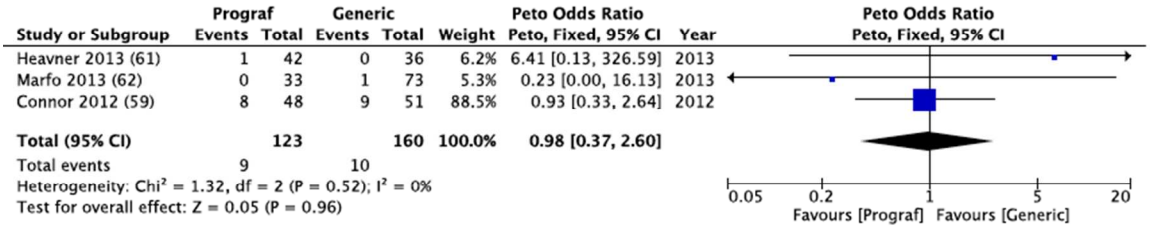
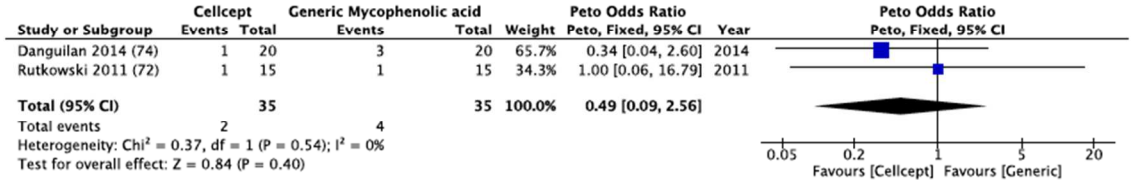


Figure 4: Cellcept acute rejection kidney observational studies



Supplementary Tables

Table 1a: Neoral study characteristics

Study, year	Country	Study Design	Transplant organ	Inclusion Criteria	Exclusion Criteria	Generic	Number of patients (total)	Mean age (Total study or B/G)
Khatami, 2013[57]	Iran	Randomized parallel group	Kidney	Incident adult transplants	Hyperoxaluria Primary focal segmental glomerulosclerosis History of malignancy in the last 5 years Re-transplant PRA >25%	Iminoral	221	38.1 (12.6)/39.3 (13.2)
Vitko, 2010[52]	Czech Republic	Randomized parallel group	Kidney	Transplanted between 1 and 10 years prior to enrollment Stable graft function No rejection in the last 6 months Stable dose of cyclosporine	None specified	Equoral	99	43.4 (11.6)/ 41.1 (12.5)
Qazi, 2006[42]	USA	Randomized parallel group (10% to Neoral and 90% to Gengraf) Before/after comparisons in Gengraf arm	Kidney	At least 6 months post transplant Stable graft function Stable cyclosporine levels	None specified	Gengraf	82	47.5 (5)
Hibberd, 2006[33]	Australia	Randomized cross over trial	Kidney	Stable transplant recipients At least 6 months post transplant	None specified	Cysporin	28	53 (10)
David-Neto, 2004[29]	Brazil	Randomized cross over trial	Kidney	Stable prevalent transplants Age 18-60 Stable cyclosporine dose	History of active cancer	Zinograf-ME	18	44.7 (12)
First, 1998[53]	USA	Randomized cross over trial	Kidney	Body weight between 45 to 155 kg	Multi-organ transplants Unstable medical	Sang-35	32	Not reported

				>6 months post transplant Stable allograft function No rejection episodes in the last 6 months No recent change in cyclosporine dose	problems			
Kim, 1998[35]	South Korea	Randomized parallel group trial	Kidney	Incident living donor transplants Adults	None specified	Neoplanta	40	40 (11.9)/ 37.2 (9.3)
Stephan, 1998[47]	USA	Randomized parallel group trial	Kidney	Incident transplants	None specified	Consupren	36	Not reported
Masri, 1996[56]	Lebanon	Randomized parallel group trial	Kidney	Prevalent transplants Unstable Sandimmune pharmacokinetics and Cmax <400 ng/ml Tmax >3.5 hrs Broad Cmax Unstable serum creatinine (>10% variation over 3 measurements)	None specified	Consupren	44	33/32
Fisher, 1999[54]	USA	Randomized cross over trial	Liver	Stable liver and renal function More than 1 year post transplant	None specified	SangCya	26	52 (10)
Leet, 2009[37]	Australia	Randomized cross over trial	Heart	At least 15 months post transplant Stable dose of cyclosporine Stable renal function No rejection in the last 6 months	Comorbidities Sirolimus use	Cysporin	16	60.06 (8.45)
Toman, 2002[50]	Czech Republic	Randomized parallel group trial	Heart	At least 6 months post transplant Clinically stable Stable cyclosporine levels	None specified	Consupren	10	51.2 (12)/ 49.8 (10)

				No significant infection				
Al Wakeel, 2008[27]	Saudi Arabia/Middle East	Interventional before/after	Kidney	Minimum transplant age of 6 months Stable graft function	None specified	Sigmasporin Microral	42	37.9 (11.1)
Al Wakeel, 2008[26]	Saudi Arabia/Middle East	Interventional before/after	Kidney	Minimum transplant age of 6 months Stable graft function	None specified	Sigmasporin Microral	75	38.9 (10.7)
Sayyah, 2007[44]	Iran	Interventional before/after	Kidney	Clinically stable for at least 2 months	Severe infections Liver dysfunction Malignancy	Iminoral	41	40.12 (13.37)
Masri, 2005[39]	Turkey, Lebanon, Pakistan	Interventional before/after	Kidney	Prevalent transplants First transplant No rejection in the past 6 months	Any of the following within 14 days of study entry: myocardial infarction, condition that might compromise GI tract, liver or kidney function, condition that might influence cyclosporine pharmacokinetics	Equoral	70	33
Fradette, 2005[32]	Canada	Interventional before/after	Kidney	At least 6 months post transplant Stable graft function	None specified	Pliva	37	49.2
Perlik, 2005[41]	Czech Republic	Interventional before/after	Kidney	Stable transplant recipients No rejection in the past 6 months	Significant co-morbidities Interacting medications	Equoral	70	Males: 35.3 Females: 34.7
Talaulikar, 2004[49]	Australia	Interventional before/after	Kidney	More than 3 months post transplant	Liver disease Instability of graft function Change of Neoral dose in the last 3 months	Cysporin	40	49.8 (11.4)
Masri, 2004[38]	Turkey, Pakistan, Lebanon, Czech Republic	Interventional before/after	Kidney	First renal transplant No rejection in the	Hepatic dysfunction CMV infection in	Equoral	Not reported	Not reported

				last 6 months Stable graft function	the last 6 months			
Durlik, 2003[31]	Poland	Interventional before/after	Kidney	At least 6 months post first renal transplant Stable graft function On Neoral for at least 3 months Age 18 to 65 years	None specified	Cicloral	42	42.5
Tsang, 2003[51]	Hong Kong	Interventional before/after	Kidney	At least 3 months post transplant On a stable dose of Neoral No interacting medications Stable graft function Age 18-65 years	Conditions or drugs that would alter cyclosporine metabolism and clearance Pregnancy	Gengraf	20	48.4 (10.7)
Roza, 2002[43]	USA	Interventional before/after	Kidney	At least 6 months post transplant Medically stable	Significant medical issues Taking drugs that influenced cyclosporine metabolism Pregnancy	Gengraf	50	49.8 (11.4)
Gaston, 1999[55]	USA	Interventional before/after	Kidney	Stable adult transplant recipients	None specified	SangCya	32	Not reported
Pamugas, 2012[40]	Philippines	Prospective cohort	Kidney	Age 18-65 years Living donor PRA <10% Incident transplants	CMV positive donor to CMV negative recipient Pulmonary TB Treatment with medications known to interact with cyclosporine	Arpimune	60	38.3 (9.3)/ 36.4 (6)
Diarra, 2010[30]	Austria	Before/after	Kidney	Stable graft function Prevalent transplants	None specified	Equoral	59	54 (16)
Kahn, 2010[34]	South Africa	Retrospective cohort with historical controls	Kidney	Prevalent transplants: stable graft function	None specified	Cicloral	Incident transplant: 49 Prevalent	Incident transplants: 39.5/ 41.9

		(incident transplants) Retrospective before/after (prevalent transplants)					transplants: 117	Prevalent transplants: Not specified
Spasovski, 2008[46]	Macedonia	Retrospective cohort	Kidney	Incident living donor recipients Neoral: 2003 Equoral: 2006	None specified	Equoral	31	38.6 (5.1)/ 39.6 (7.6)
Sharma, 2006[45]	India	Prospective cohort	Kidney	Incident transplants from November 2003 to March 2005	None specified	Arpimune	37	28.1 (9.5)/ 30.55 (9.8)
Taber, 2005[48]	USA	Retrospective cohort	Kidney	Incident transplants Neoral group: Transplanted between January 1999 and May 2001 Gengraf group: transplanted between May 2001 and July 2002	Graft failure within 14 days post transplant Incomplete data collection	Gengraf	188	48.7/ 51.2
Carnahan, 2003[28]	USA	Prospective before/after	Kidney	Prevalent transplants	Already taking another generic preparation	Gengraf	46	50.5
Kraeuter, 2013[36]	Germany	Retrospective before/after	Heart	Clinically stable adult chronic transplant patients transplanted from 1989 to 2009	No rejection episodes at the time of conversion Lack of patient adherence Multi-organ transplants	Equoral	20	60.7 (10)

B/G: B=Brand name; G= Generic

Table 1b: Prograf study characteristics

Study, year	Country	Study Design	Transplant organ	Inclusion Criteria	Exclusion Criteria	Generic	Number of patients (total)	Mean age (Total study or B/G)
Robertsen, 2014[69]	Norway	Randomized cross over trial	Kidney	Incident transplants 60 years of age or older	None specified	Tacni	25	69 (60-78)*
Min, 2013[63]	South Korea	Randomized parallel group trial followed by a crossover trial at 6 months in a subset of patients	Kidney	Adult incident transplant patients (living or deceased)	Kidney from donors after cardiac death Infection Liver disease Previous non renal transplant Malignancy within 5 years	Tacrobell	126	45.6 (12.4) / 47 (12.7)
Alloway, 2012[58]	USA	Randomized cross over trial	Kidney	At least 6 months post transplant On a stable dose of tacrolimus	None specified	Sandoz	71	52 (12.5)
Rosenborg, 2014[64]	Sweden	Interventional before/after	Kidney	Stable renal function Inclusion from January to December 2012	New transplants Active neoplasm	Sandoz	67	57.6 (11)

McDevitt-Potter, 2011[67]	USA	Interventional before/after	Liver, Kidney, multiorgan	On a stable tacrolimus dose Prevalent transplants	Changing tacrolimus trough target Non adherent with monitoring On a mixture of generic and brand products	Sandoz	70 Liver n=28 Kidney n=27 Multiorgan n=5	52 (12)
Heavner, 2013[61]	USA	Retrospective cohort	Kidney	Prograf group: admission to hospital from October to December 2009 Generic group: admission from December 2009 to February 2009	Transplant within 90 days of admission New initiation of tacrolimus	Sandoz	78	51 / 54
Marfo, 2013[62]	USA	Retrospective before/after and retrospective cohort	Kidney	Switched from brand-name to generic between 2009 and 2010	Less than 3 months post transplant	Any generic	Before/after: 73 Cohort: 106	51 (16) / 54 (13)
Connor, 2012[59]	United Kingdom	Retrospective cohort	Kidney	Incident transplant patients Prograf: Transplanted between November 2009 and November 2010 Generic: Transplanted between November 2010 and 2011	None specified	Adoport	99	52 / 57*
Momper, 2011[68]	USA	Retrospective before/after	Liver, kidney	Liver: at least 6 months post transplant Kidney: at least 3 months post transplant Conversion between August	Non adherent with drug level monitoring Co-prescribed interacting medications	Sandoz	103 Liver: 48 Kidney: 55	Liver: 60.6 (10.9) Kidney: 49.9 (15.1)

				2009 to April 2010				
Spence, 2012[65]	USA	Retrospective before/after	Liver, kidney, heart	Clinically stable with conversion to generic between October 1st to December 31st, 2010	None specified	Sandoz	Liver: 29 Kidney: 193 Heart: 12	54 (12.9)
Yu, 2012[66]	South Korea	Prospective cohort with historical controls	Liver	Incident transplants	Over age 65 Severe infection	Tacrobell	117	51.2 (4.8)/ 48.7 (6.9)
Dhungel, 2013[60]	USA	Retrospective cohort with historical controls	Heart	Incident transplants	None specified	Generic not specified	65	50.9 (16.5)/ 56.8 (10.2)

B/G: B=Brand name; G= Generic

*Median (range)

Table 1c: Cellcept study characteristics

Study, year	Country	Study Design	Transplant organ	Inclusion Criteria	Exclusion Criteria	Generic	Number of patients (total)	Mean age (Total study or B/G)
Sunder-Plassmann, 2012[73]	Multi-centre, International	Randomized cross over trial	Kidney	At least 12 months post transplant Stable renal function	None specified	Myfenax	43	50.7 (13.5)
Abdallah, 2010[70]	Tunisia	Randomized parallel group trial	Kidney	All incident transplants between January 2007 and December 2008	None specified	Mycophenolate mofetil 500 (Medis, Tunisia)	18	33.3 (11.7)/ 36.3 (7.1)
Videla, 2007[75]	Chile	Interventional before/after	Kidney	Stable renal function	None specified	Linfonex	5	Not reported
Danguilan, 2014[74]	Philippines	Prospective cohort with historical controls	Kidney	18-65 years of age Incident transplants Primary kidney transplant from a living donor PRA <10%	None specified	Mycept	56	Not reported 90% of patients between the ages 20-40
Rutkowski, 2011[72]	Poland	Cohort	Kidney	Incident transplants from April 2009 to January 2011 (partner kidneys)	None specified	Myfenax	15	49/54.1

Namgoong, 2013[71]	South Korea	Prospective before/after	Liver	Transplant 2 years or more before the study with stable function	None specified	Myconol	53	55.9 (7.1)

Table 2: Quality assessment of non-randomized studies

Study	Comparison of each intervention occurred		Method used to form intervention groups	Retrospective (R) or prospective (P) study design	Confounding considered in the study design or analysis	Did the study have a protocol?*	Outcome of acute rejection			Outcome of drug levels/bioequivalence		
	Between two or more groups of participants	Within the same group of participants over time					Pre-specified objective	Measured	Analyzed**	Pre-specified objective	Measured	Analyzed
Al Wakeel 2008[27]	N	Y	Action of researchers	P	N	Y	N	N	N	Y	Y	Y
Al Wakeel 2008[26]	N	Y	Action of researchers	P	N	Y	Y	Y	N	Y	Y	Y
Sayyah, 2007[44]	N	Y	Action of researchers	P	N	Probably yes	N	N	N	Y	Y	Y
Masri, 2005[39]		Y	Action of researchers	P	N	Probably yes	N	N	N	Y	Y	Y
Fradette, 2005[32]	N	Y	Action of researchers	P	Y Multivariable regression	Probably yes	N	N	N	Y	Y	Y
Perlik, 2005[41]	N	Y	Action of researchers	P	N	Y	N	N	N	Y	Y	Y
Talaulikar, 2004[49]	N	Y	Action of researchers	P	N	Y	N	N	N	Y	Y	Y
Masri, 2004[38]	N	Y	Action of researchers	P	N	Y	N	N	N	Y	Y	Y
Durlik, 2003[31]	N	Y	Action of researchers	P	N	Y	N	N	N	Y	Y	Y
Tsang, 2003[51]	N	Y	Action of researchers	P	N	Probably yes	Y	Y	N	Y	Y	Y
Roza, 2002[43]	N	Y	Action of researchers	P	N	Y	Y	Y	N	Y	Y	Y
Gaston, 1999[55]	N	Y	Action of researchers	P	N	Probably yes	Y	Y	N	Y	Y	Y
Pamugas, 2012[40]	Y	N	Unclear	P	Y Matching on age, sex, primary renal disease, number of DR mismatches	Probably yes	Y	Y	N	Y	Y	Y
Diarra 2010[30]	N	Y	Healthcare decision makers and participant preferences	Unclear	N	Probably no	N	N	N	Y	Y	Y
Kahn, 2010 Incident	Y	N	Time differences	R	N	Probably yes	N	Y	N	Y	Y	Y

transplants sub-study[34]			and healthcare decision makers									
Kahn, 2010 Prevalent transplants sub-study[34]	N	Y	Time differences and healthcare decision makers	R	N	Probably yes	N	Y	N	Y	Y	Y
Spasovski, 2008[46]	Y	N	Time differences	R	Y Matching on age, gender and body weight	Probably no	Y	Y	Y	Y	Y	Y
Sharma, 2006[45]	Y	N	Unclear	P	Y Matching on age and sex No differences in other key baseline characteristics	Probably no	Y	Y	Y	Y	Y	Y
Taber, 2005[48]	Y	N	Time differences	R	Y No differences in baseline characteristics	Y	Y	Y	Y	N	N	N
Carnahan, 2003[28]	N	Y	Healthcare decision makers (Medical centre formulary changes)	P	N	Probably yes	Y	Y	N	Y	Y	Y
Kraeuter, 2013[36]	N	Y	Participant preferences	R	N	Probably yes	Y	Y	Y	Y	Y	Y
Rosenborg, 2014[64]	N	Y	Healthcare decision makers	P	Y To account for dose adjustments drug levels were normalized for dose	Probably yes	Y	Y	N	Y	Y	Y
Mcdevitt-Potter, 2011[67]	N	Y	Healthcare decision makers, location differences and participant preferences	P	N	Probably yes	Y	Y	N	Y	Y	Y
Heavner, 2013[61]	Y	N	Time differences	Unclear	N	Y	Y	Y	N	Y	Y	Y
Marfo, 2013[62]	Y	Y	Retail	R	N	Y	Y	Y	N	Y	Y	Y

			pharmacy switch									
Connor, 2012[59]	Y	N	Healthcare decision makers and time differences (program switch due to cost)	R	Y Matching on immunosuppression and deceased vs living donor	Probably no	Y	Y	Y	Y	Y	Y
Momper, 2011[68]	N	Y	Unclear	R	Y Multivariable regression	Probably yes	Y	Y	N	Y	Y	Y
Spence, 2012[65]	N	Y	Healthcare decision makers	R	N	Y	Y	Y	N	Y	Y	Y
Yu, 2012[66]	Y	N	Time and location differences (historical controls)	P (generic group) R (brand name group)	Y Matching on age, disease type, gender, liver disease severity, graft to recipient weight ratio	Probably yes	Y	Y	Y	Y	Y	Y
Dhungel, 2013[60]	Y	N	Time differences (historical controls)	R	N	Probably no	Y	Y	Y	Y	Y	Y
Videla, 2007[75]	N	Y	Action of researchers	P	N	Probably yes	N	N	N	Y	Y	Y
Danguilan, 2014[74]	Y	N	Time differences (historical controls)	P (generic group) R (brand name group)	Y Matching on age, gender, PRA and HLA typing	Probably yes	Y	Y	Y	Y	Y	Y
Rutkowski, 2011[72]	Y	N	Unclear	Unclear	Y Matched based on donor (partner kidneys)	Probably no	Y	Y	Y	Y	Y	N
Namgoong, 2013[71]	N	Y	Healthcare decision makers and time differences (program was switching from trade name to generic)	P	N	Probably yes	Y	Y	N	Y	Y	Y

*Did the study have a protocol? An answer of probably yes was given if the methods specified that the study received REB or IRB approval or if the study was interventional, but it was not specifically stated that the study had a protocol. An answer of probably no was given if there was no specific statement about REB/IRB approval or a protocol and the study was observational.

**The outcome of acute rejection was often not analyzed due to a lack of events.

Table 3a: Neoral pharmacokinetic outcomes

Study, year, organ	Dose adjustments allowed (y/n)	One to one dose conversion (y/n)*	Number of patients with dose adjustments (B/G)§	Time of outcome measurement	Dose* (mg/d)		Weight normalized dose (mg/kg/d)		Trough level (C0) (ng/ml)		C2 (ng/ml)		AUC (0-4) (ng/ml)* h		AUC (0-12) (ng/ml)* h		Cmax (ng/ml)		Tmax (h)		Cmax mean ratio (90% CI)	AUC mean ratio (90% CI)
					B	G	B	G	B	G	B	G	B	G	B	G	B	G	B	G	B	G
Khatami, 2013, kidney[57]	Y	N/A	Unclear	12 months post transplant			2.8 (1.1)	2.6 (1.1)	152.8 (56.3)	176.1 (81.2)	675.59 (226.2)	725.0 (280.9)										
Vitko, 2010, kidney[52]	Y	Y	Unclear	180 days post randomization	205.64 (85.0)	208.5 (97.6)			130.48 (26.1)	138.08 (32.22)	669.13 (133.83)	669.13 (133.83)										
Qazi, 2006, kidney[42]	Y	Y	0/13¶	2 weeks post randomization					185 (98)	195 (81)												
Hibberd, 2006, kidney[33]	Unclear	Y	Unclear	Days 14 and 28											3853.4 (1377.8)	3494.6 (1319.2)	880.9 (368.2)	754.8 (301.4)	1.4 (0.6)	1.9 (0.8)	0.88 (0.8-0.97)	0.93 (0.88-0.98)
David-Neto, 2004, kidney[29]	N	Y	N/A	Day 0 and day 7					156 (81)	160 (78)	734 (229)	708 (225)			3971 (1326)	4020 (1467)	1022 (357)	999 (377)	1.3 (0.3)	1.4 (0.3)	0.977	1.012
First, 1998, kidney[53]	N	Y	N/A	One week											4377 (1579)	4120 (1508)	994 (391)	890 (332)	1.3 (0.4)	1.4 (0.6)	0.93 (0.84-1.02)	0.95 (0.86-1.05)
Stephan, 1998, kidney[47]	Y	N/A	Unclear	One month post transplant			6.55 (1.29)	6.85 (1.37)	245 (92.4)	296 (82)							1123 (256)	1055 (248)	1.81 (0.39)	1.80 (0.4)		
Kim, 1998, kidney[35]	Unclear	N/A	Unclear	Unclear when measured Total study duration 4 weeks											6528.3 (1087.6)	7274.2 (1805)	1650 (30.69)	1709.6 (24.9)	1.4 (0.4)	1.4 (0.4)		
Masri, 1996, kidney[56]	Y	Unclear	19/18	One week post randomization			3.61 (1.42)	3.79 (1.46)	165.3 (36.4)	158.1 (47.9)							795.2 (247)	638.3 (167.9)				
Fisher, 1999, liver[54]	Unclear	Y	Unclear	Unclear					143 (54)	147 (58)					3572 (1448)	3397 (957)	589 (288)	503 (146)	2.9 (1.6)	3.1 (1.2)	0.93 (0.81-1.06)	0.99 (0.89-1.09)
Leet, 2009, heart[37]	Unclear	Y	Unclear	14 days on each medication																	1.30 (1.20-1.42)Ψ	1.17 (1.11-1.23)Ψ
Toman, 2002, heart[50]	Y	Y	11 (4/7)	12 weeks after randomization					148 (34.3)	196.2 (88.5)												

Diarra, 2010, kidney[30]	Unclear	Unclear	Unclear	Pre conversion and 6 months post conversion	152.7 (50.9)	152.0 (52.2)			87.53 (47.44)	81.51 (25.72)												
Al Wakeel, 2008, kidney[27]	N	Y	N/A	Pre conversion and 14 days post conversion					117.2 (62.8)	115.6 (62.8)					3778.6 (1610.5)	3634.4 (1419.1)	970.6 (39.7)	898.4 (346.5)	1.6 (0.7)	1.5 (0.7)	0.93 (0.8573-1.0358)	0.96 (0.9256-1.0355)
Al Wakeel, 2008, kidney[26]	Y	Y	2¶	Pre conversion and 14 days post conversion					171.1 (103.3)	177.1 (117.1)	760.3 (387.2)	706.5 (275.1)										
Sayyah, 2007, kidney[44]	Y	Y	0	Pre conversion and 5 days post conversion					235.16 (144.89)	193.17 (99.58)												
Masri, 2005, kidney[39]	Unclear	Y	Unclear	14 days pre and post conversion					109.8 (14.41)	109.3 (17.26)	680.5 (0.5)	689 (6)			2856	2892	773	743			(0.93-1.01)	(0.99-1.06) Only CI reported
Perlik, 2005, kidney[41]	N	Y	N/A	C0 and C2: 2 weeks pre conversion and 3 days post conversion AUC and Cmax: pre conversion and 14 days post conversion					123	114	604	591			3039	3108	725	717			0.99 (0.93-1.05)	1.02 (0.99-1.06)
Fradette, 2005, kidney[32]	Unclear	Y	Unclear	14 days pre and post conversion											3354.67 CV% (32.3)	3243.63 CV% (42.3)	841.06 CV% (36)	807.04 CV% (43.1)			0.96 (0.886-1.061)	0.981 (0.93-1.036)
Talaulikar, 2004, kidney[49]	Unclear	Y	Unclear	Pre conversion and 2 weeks post conversion					106 (48-188)**	98 (33-200)**	660 (73-1170)**	736 (106-1096)**	1730 (861-2980)**	2180 (858-2750)**	3000 (1490-5150)**	3840 (1310-5090)**						1.01 (0.94-1.1)Ψ
Masri, 2004, kidney[38]	Unclear	Y	Unclear	C0 and C2: 7 days apart AUC and Cmax: days 14 and 28					109.8 (14.41)	109.3 (17.26)	680.5 (0.5)	689 (6)			2856	2892	773	743				
Carnahan, 2003, kidney[28]	Y	Y	Unclear for the whole group, 2 for subgroup >18	Pre conversion and at least 2 weeks post conversion					139	156												

			months post transplant																		
Durlik, 2003, kidney[31]	Unclear	Y	Unclear	Pre conversion and 2 weeks post conversion					155 (31)	138 (30)					4421 (647)	3834 (767)					
Tsang, 2003, kidney[51]	Y	Y	0	Days 1 and 8 (Neoral) Days 21 and 28 (generic)					127 (50.1)	142.6 (49.1)	728 (220)	913.3 (359.7)	2421 (722)	2637 (846)			1007 (358)	1101.9 (425.6)	1.53 (0.72)	1.8 (0.9)	1.09 (0.97-1.2)	1.09 (0.97-1.2)
Roza, 2002, kidney[43]	Y	Y	0	C0: Pre and 2 weeks post conversion AUC, Cmax and Tmax: Days 14 and 28					198 (77)	198 (80)					5016 (1648)	5008 (1767)	1247 (405)	1246 (477)	1.5 (0.4)	1.6 (0.5)	0.981 (0.922-1.044)	0.992 (0.951-1.034)
Gaston, 1999, kidney[55]	N	Y	N/A	Pre conversion and one week post conversion											4377 (1579)	4120 (1508)	994 (391)	890 (332)	1.3 (0.4)	1.4 (0.6)	0.93 (0.84-1.02)	0.95 (0.86-1.05)
Pamugas, 2012, kidney[40]	Y	N/A	Unclear	AUC (0-4), Cmax, Tmax: 4 days post transplant Other outcomes: one month post transplant	251.7 (83.5)	275.8 (67.9)					1563.5 (621)	1455.1 (305)	3169.7 (0.356)	3663.1 (0.352)			1152.32	1451.64	2.0 (0.3)	1.87 (0.27)	0.968 (0.900-1.127)Ψ	0.988 (0.953-1.08)Ψ
Kahn, 2010, kidney, incident transplants[34]	Y	N/A	Unclear	One week post transplant	268	283			192	213												
Kahn, 2010, kidney, stable transplant[34]	Y	Y	Unclear	One month pre and post conversion	53 (4)	56 (4)			133 (7)	132 (8)												
Spasovski, 2008, kidney[46]	Y	N/A	Unclear	6 months post transplant	147.8 (29.9)	191.7 (4.1)					793.2 (139.8)	597.7 (93.4)										
Sharma, 2006, kidney[45]	Y	N/A	Unclear	3 months			5.9 (2.2)	6.2 (1.4)			1342.4 (303.4)	1306.7 (254.4)										
Kraeuter, 2013, heart[36]	Y	Y	17	8 months pre and post conversion	140.67 (39.81)	134.58 (41.61)			102.2 (39.6)	79.7 (24.9)												

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*Listed as N/A (not applicable) if the study was a parallel group trial or cohort study in incident transplants. Dose is only reported for studies that allowed dose adjustments and where values for the brand name and generic groups were clearly reported.

§Reported as total number of dose changes post conversion from brand name to generic or as total number in the brand name group and total number in the generic group (B/G), where B=brand name and G=generic
¶Dose adjustments occurred after measurement of outcome
Ψmean ratio and 95% confidence interval
**median (IQR)
CV= coefficient of variation
C2= drug level 2 hours after administration
AUC= area under the curve
Cmax= maximum concentration
An empty cell indicates that the outcome was not reported

Table 3b: Prograf pharmacokinetic outcomes

Study, year, organ	Dose adjustments allowed (y/n)	One to one dose conversion (y/n)*	Number of patients with dose adjustments (B/G)§	Timing of outcome measurements	Dose (mg/d)*		Weight normalized dose (mg/kg/d)		Concentration: dose ratio (ng/ml)/(mg/kg/d)		Trough level (ng/ml)		AUC (0-12) (ng/ml)* h		Cmax (ng/ml)		Tmax (h)		Cmax mean ratio (90% CI)	AUC mean ratio (90% CI)	Trough level ratio (90% CI)
					B	G	B	G	B	G	B	G	B	G	B	G	B	G			
Robertsen, 2014, kidney[69]	N	Y	N/A	6 weeks post transplant and 7-10 days post conversion							6.6 (1.4)	6.6 (1.5)	115 (27)	136 (38)	19.6 (6.3)	30.2 (11.6)	1.4 (0.7)	1.1 (0.5)	1.49 (1.35-1.65)	1.17 (1.10-1.24)	0.99 (0.92-1.06)
Min, 2013, kidney[63]	Y	Y	Unclear	6 months			0.086 (0.04)	0.069 (0.03)			6.89 (2.2)	5.65 (1.6)	118.5 (34.2)	106.8 (34.7)	19.6 (7.4)	19.6 (9.5)	1.4 (0.8)	1.0 (0.5)	1.145 (1.012-1.523)	1.098 (0.93-1.38)	
Alloway, 2012, kidney[58]	N	Y	N/A	Days 14 and 28							7.0 (2.1)	7.3 (1.8)	60 (37.8)	61.8 (40.6)	9.1 (5.5)	9.6 (5.5)	1.9 (1.3)	1.5 (1.1)	1.09 (1.01-1.18)	1.02 (0.97-1.08)	
Rosenberg, 2014, kidney[64]	Y	Y	(12/8)	4 weeks pre and post conversion							4.8 (4.5-5.0)Ψ	4.9 (4.6-5.2)Ψ									
McDevitt-Potter, 2011, kidney, liver, multi-organ[67]	Y	Y	20 (5/15)¶	Dose: Pre and post conversion Level: 3 most recent levels before conversion compared to first level 4-7 days post conversion	4.4 (3.2)	4.5 (2.9)					5.8 (2.1)	5.9 (2.7)									
Heavner, 2013, kidney[61]	Y	Y	(22/22)	Median level during a hospital admission							7.4	6.2									
Marfo, 2013, kidney[62]	N	Y	N/A	90 days pre and post conversion							6.8 (2.2)	6.0 (1.6)									
Connor, 2012, kidney[59]	Unclear	N/A	Unclear	One month post transplant							9.39 (8.19-10.75)**	8.66 (7.93-9.46)**									
Spence, 2012, kidney, liver, heart[65]	Y	Unclear	36-all post conversion to generic. Except for dose, outcomes were measured prior to any dose changes.	Dose: Pre conversion compared to last observed dose post conversion (average follow up 206 days) Other outcomes: On average 32 days pre conversion and 22 days post conversion	4.98 (3.37)	4.99 (3.51)					Kidney: 6.79 (1.62) Liver: 6.5 (1.53) Heart: 6.36 (1.74)	Kidney: 6.97 (2.37) Liver: 6.98 (2.14) Heart: 6.73 (1.64)									Kidney: 1.00 (0.96-1.04) Liver: 1.05 (0.96-1.15) Heart: 1.06 (0.99-1.15)

Momper, 2011, kidney, liver[68]	Y	Y	43 (kidney and liver not presented separately)	Average pre and post conversion over 50 days			Kidney: 0.087 Liver: 0.039	Kidney : 0.091 Liver: 0.041	Kidney: 125.3 (92.7) Liver: 184.1 (123.2)	Kidney: 110.4 (79.2) Liver: 154.7 (87.8)											Kidney: (0.904-0.966 Liver: (0.869-0.957). Only CI's reported.
Yu, 2012, liver[66]	Y	N/A	Unclear	Initial dose	5.8 (4.1)	5.1 (3.3)															
Dhungel, 2012, heart[60]	Y	N/A	Unclear	Mean level over 6 months post transplant							7.9 (1.8)	8.8 (1.8)									

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§Reported as total number of dose changes post conversion from trade name to generic or as total number in the brand name group and total number in the generic group (B/G), where B=brand name and G=generic
¶Dose adjustments occurred after measurement of outcomes
Ψmean and 95% confidence interval
**median (IQR)
CV= coefficient of variation
AUC= area under the curve
Cmax= maximum concentration
An empty cell indicates that the outcome was not reported

Table 3c: Cellcept pharmacokinetic outcomes

Study, year, organ	Dose adjustments allowed (y/n)	One to one dose conversion (y/n)*	Number of patients with dose changes (B/G)§	Timing of outcome measurements	Pre dose 12 h MPA (µg/ml)		AUC (0-3) (µg/ml)* h		AUC (0-6) (µg/ml)* h		AUC (0-12) (µg/ml)* h		Cmax (µg/ml)		Tmax (h)		Cmax mean ratio (90% CI)	AUC mean ratio (0-6) (90% CI)	AUC mean ratio (0-12) (90% CI)
					B	G	B	G	B	G	B	G	B	G	B	G			
Sunder-Plassman, 2012, kidney[73]	Unclear	Unclear	Unclear	Study day 1, 14, 28, 70, 112	2.69 (1.7)	3.00 (2.09)			33.52 (15.13)	31.10 (15.42)	49.85 (20.83)	48.26 (21.22)	16.19 (9.95)	14.31 (8.34)	1.12 (0.75)	1.34 (1.14)	0.873 (0.787-0.968)	0.923 (0.865-0.984)	0.959 (0.899-1.023)
Abdallah, 2010, kidney[70]	Unclear	N/A	Unclear	Study days 0, 7, 30, 90 and 180			27.76	26.12											
Videla, 2007, kidney[75]	Unclear	Y	Unclear	Pre conversion and 60 days post conversion	3.36 (1.41)	3.84 (0.62)			22.69 (13.7)	24.81 (6.67)									
Danguilan, 2014, kidney[74]	N	N/A	0	Unclear			38.21	36.78					7.88	6.92	1.07	1.03			
Rutkowski, 2011, kidney[72]	Y	N/A	(11/8)¶	Unclear	7.15	6.70													
Namgoong, 2013, liver[71]	Unclear	Y	Unclear	3 months pre and post conversion	1.71 (0.88)	1.83 (0.91)													

All continuous variables are reported as mean and standard deviation (SD) unless otherwise specified
*Listed as N/A (not applicable) if the study was a parallel group trial or cohort study. Dose is only reported for studies that allowed dose adjustments and where values for the trade name and generic groups were reported.
§Reported as total number of dose changes post conversion from trade name to generic or as total number in the brand name group and total number in the generic group (B/G), where B=brand name and G=generic
¶Dose adjustments occurred after measurement of outcomes
Ψmean and 95% confidence interval
**median (IQR)
CV= coefficient of variation
AUC= area under the curve
Cmax= maximum concentration
MPA= mycophenolic acid
An empty cell indicates that the outcome was not reported

Table 4a: Neoral clinical outcomes

Outcome	Study, year, organ	Definition of acute rejection	Trial (y/n)	Follow up time	Number of patients analyzed (B/G)	Neoral	Generic
Acute Rejection	Khatami, 2013, kidney[57]	Clinical +/- biopsy	Y	1 year	221 (110/111)	16	16
	Vitko, 2010, kidney[52]	Unclear	Y	180 days	99 (52/47)	0	0
	Kim, 1998, kidney[35]	Unclear	Y	4 weeks	40 (20/20)	2	1
	Stephan, 1998, kidney[47]	Unclear	Y (but only 40 were randomized)	1 year	52 (20/32)	6 biopsied 9 presumed	5 biopsied 14 presumed
	Leet, 2009, heart[37]	Biopsy proven	Y	4 weeks	16	0	0
	Toman, 2002, heart[50]	Biopsy proven	Y	12 weeks	11 (6/5)	0	0
	Al Wakeel, 2008, kidney[26]	Clinical +/- biopsy	N	6 months	75	8	2
	Sayyah, 2007, kidney[44]	Unclear	N	6 months	41	0	0
	Carnahan, 2003, kidney[28]	Unclear	N	Average follow up 18 weeks	41	0	0
	Tsang, 2003, kidney[51]	Unclear	N	4 weeks	20	0	0
	Roza, 2002, kidney[43]	Unclear	N	29 days (2 weeks on each)	50	0	0
	Pamugas, 2012, kidney[40]	Biopsy proven	N	6 months	60 (30/30)	4	2
	Spasovski, 2008, kidney[46]	Unclear	N	6 months	31 (16/15)	4	9
	Sharma, 2006, kidney[45]	Biopsy proven	N	1 year	37 (17/20)	8	6
	Taber, 2005, kidney[48]	Biopsy proven	N	6 months	188 (100/88)	25	34
	Kraeuter, 2013, heart[36]	Biopsy proven	N	8 months	20	0	0
Graft loss (n)	Khatami, 2013, kidney[57]		Y	1 year	221 (110/111)	1	0
	Kim, 1998, kidney[35]		Y	4 weeks	40 (20/20)	0	0
	Stephan, 1998,		Y	1 year	52 (20/32)	0	0

	kidney[47]						
	Al Wakeel, 2008, kidney[26]		N	6 months	75	0	0
	Pamugas, 2012, kidney[40]		N	6 months	60 (30/30)	0	0
	Sharma, 2006, kidney[45]		N	1 year	37 (17/20)	1	0
	Toman, 2002, heart[50]		Y	12 weeks	11 (6/5)	0	0
	Kraeuter, 2013, heart[36]		N	8 months	20	0	0
Death (n)	Khatami, 2013, kidney[57]		Y	1 year	221 (110/111)	1	1
	Vitko, 2010, kidney[52]		Y	180 days	99 (52/47)	1	0
	Stephan, 1998, kidney[47]		Y	1 year	52 (20/32)	0	0
	Al Wakeel, 2008, kidney[26]		N	6 months	75	0	0
	Roza, 2002, kidney[43]		N	29 days	50	0	0
	Pamugas, 2012, kidney[40]		N	6 months	60 (30/30)	0	1
	Sharma, 2006, kidney[45]		N	1 year	37 (17/20)	0	0
	Toman, 2002, heart[50]		Y	12 weeks	11 (6/5)	0	0
	Kraeuter, 2013, heart[36]		N	8 months	20	0	0
Infection (n)	Khatami, 2013, kidney[57]		Y	1 year	221 (110/111)	7	9
	Vitko, 2010, kidney[52]		Y	180 days	99 (52/47)	7	7
	Fradette, 2005, kidney[32]		N	35 days	37	2	1
	Pamugas, 2012, kidney[40]		N	6 months	60 (30/30)	8	4
	Toman, 2002, heart[50]		Y	12 weeks	11 (6/5)	0	1
eGFR (ml/min/1.73m2)	Pamugas, 2012, kidney[40]		N	6 months	60 (30/30)	62.03 (12.1)	74.02 (15.8)
	Kraeuter, 2013, heart[36]		N	8 months	20	59.93 (21.98)	59.57 (20.23)
Serum creatinine	Khatami, 2013, kidney[57]		Y	1 year	221 (110/111)	117.5 (53.0)	107.8 (17.6)

(µmol/L)	Qazi, 2006, kidney[42]		Y (randomized to switch to generic *vs* no switch)	4 weeks post randomization	82 (9/73)	153.82 (106.08)	146.74 (43.32)
	First, 1998, kidney[53]		Y	3 weeks	32	123.76 (35.36)	123.76 (35.36)
	Kim, 1998, kidney[35]		Y	1 week	40 (20/20)	118.46 (37.13)	101.66 (15.03)
	Stephan, 1998, kidney[47]		Y	6 months	52 (20/32)	107.85 (21.22)	106.96 (18.56)
	Masri, 1996, kidney[56]		Y	One year post randomization	44 (21/23)	140.56 (35.36)	129.06 (29.17)
	Diarra, 2010, kidney[30]		N	1 month	59	165.48 (89.77)	164.48 (89.0)
	Diarra, 2010, kidney[30]		N	3 months	59	165.48 (89.77)	167.82 (100)
	Diarra, 2010, kidney[30]		N	6 months	59	165.48 (89.77)	176.41 (119.43)
	Al Wakeel, 2008, kidney[26]		N	6 months	75	116.1 (29.5)	119.8 (32.1)
	Sayyah, 2007, kidney[44]		N	6 months pre and post conversion	41	123.76 (42.4)	118.46 (35.4)
	Masri, 2005, kidney[39]		N	Pre conversion and 7 days post conversion	70	108.73	109.62
	Masri, 2004, kidney[38]		N	21 days	Unclear	108.73	109.62
	Carnahan, 2003, kidney[28]		N	2 weeks	41	151.16	148.51
	Tsang, 2003, kidney[51]		N	2 weeks	20	120.4 (41.3)	118.5 (43.1)
	Roza, 2002, kidney[43]		N	2 weeks	50	115.80 (41.55)	114.04 (38.98)
	Pamugas, 2012, kidney[40]		N	6 months	60 (30/30)	108.73 (38.90)	99.01 (22.10)
	Kahn, 2010, kidney, prevalent transplants[34]		N	1 month pre and post conversion	117	142 (6)	135 (5)
	Spasovski, 2008, kidney[46]		N	6 months	31 (16/15)	127.5 (43.5)	155.5 (68.6)
	Sharma, 2006,		N	1 year	37 (17/20)	132.6 (141.44)	123.76 (53.04)

	kidney[45]						
	Kraeuter, 2013, heart[36]		N	8 months	20	113.15 (29.17)	112.27 (32.71)

All continuous variables are reported as mean and standard deviation (SD) unless otherwise specified
B/G, B=brand name, G=generic

Table 4b: Prograf clinical outcomes

Outcome	Study, year, organ	Definition of acute rejection	Trial	Follow up time	Number of patients analyzed (B/G)	Prograf	Generic
Acute rejection	Min, 2013, kidney[63]	Biopsy proven with clinical evidence	Y	6 months	93 (38/55)	2	2
	Alloway, 2012, kidney[58]	Unclear	Y	28 days	71	0	0
	Rosenborg, 2014, kidney[64]	Unclear	N	4 weeks	67	0	0
	McDevitt-Potter, 2011, kidney, liver, multiorgan[67]	Biopsy proven	N	Unclear	70	0	0
	Heavner, 2013, kidney[61]	Biopsy proven	N	6 months	78 (42/36)	1	0
	Marfo, 2013, kidney[62]	Biopsy proven	N	1 year	106 (33/73)	0	1
	Connor, 2012, kidney[59]	Biopsy proven	N	6 months	99 (48/51)	8	9
	Spence, 2012, kidney, liver, heart[65]	Biopsy proven	N	106 days	234	0	0
	Momper, 2011, kidney, liver[68]	Unclear	N	Average 50 days	103	0	0
	Yu, 2012, liver[66]	Biopsy proven	N	26 weeks	117 (60/57)	5	0
Acute cellular rejection 1R (mean episodes/ patient day)	Dhungel, 2012, heart[60]	Biopsy proven	N	6 months	65 (44/21)	0.022 (0.01)	0.023 (0.01)
Acute cellular rejection 2R (mean episodes/ patient day)	Dhungel, 2012, heart[60]	Biopsy proven	N	6 months	65 (44/21)	0.0002 (0.001)	0.0011 (0.0025)
Acute cellular rejection 3R (mean episodes/ patient day)	Dhungel, 2012, heart[60]	Biopsy proven	N	6 months	65 (44/21)	0.0002 (0.001)	0
Graft loss	Min, 2013, kidney[63]		Y	6 months	93 (38/55)	0	0

	Alloway, 2012, kidney[58]		Y	28 days	71 (36/35)	0	0
	Connor, 2012, kidney[59]			6 months	99 (48/51)	6	8
	Yu, 2012, liver[66]		N	6 months	117 (60/57)	0	0
Death	Min, 2013, kidney[63]		Y	6 months	93 (38/55)	1	0
	Connor, 2012, kidney[59]		N	6 months	99 (48/51)	2	2
	Spence, 2012, kidney, liver, heart[65]		N	106 days	234	0	0
	Yu, 2012, liver[66]		N	6 months	117 (60/57)	0	0
	Dhungel, 2012, heart[60]		N	6 months	65 (44/21)	2	2
Infection	Min, 2013[63]		Y	6 months	126 (63/63)	10	8
	Marfo, 2013, kidney[62]		N	90 days	73	10	12
	Connor, 2012, kidney[59]		N	6 months	99 (48/51)	4**	4**
	Dhungel, 2012, heart[60]		N	6 months	65 (44/21)	8	1
eGFR (ml/min/1.73m2)	Min, 2013, kidney[63]		Y	6 months	93 (38/55)	66.3 (18.5)	64.4 (16.7)
	Rosenborg, 2014, kidney[64]		N	4 weeks	67	51 (47-55)#	51 (47-55)#
	Connor, 2012, kidney[59]		N	6 months	99 (48/51)	54.3 (20.2)	47.4 (15.2)
Serum creatinine (µmol/L)	Rosenborg, 2014, kidney[64]		N	4 weeks	67	129 (118-140)#	131 (119-143)#
	Marfo, 2013, kidney[62]		N	90 days	73	133.48 (48.62)	137.02 (58.34)
	Connor, 2012, kidney[59]		N	6 months	99 (48/51)	127 (111.8-157.2)*	112 (96-167)*
	Spence, 2012, kidney, liver, heart[65]		N	106 days	234	117.57 (42.43)	120.22 (72.49)
	Momper, 2011, kidney[68]		N	Average 50 days	55	136.14 (68.95)	134.37 (69.84)
	Momper, 2011, liver[68]		N	Average 50 days	48	142.32 (109.62)	144.09 (116.69)

All continuous variables are reported as mean and standard deviation (SD) unless otherwise specified
mean (95% confidence interval)

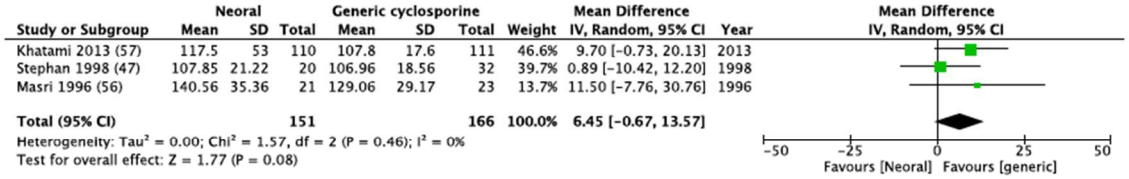
*median (IQR)
**CMV disease
B/G, B=brand name, G=generic

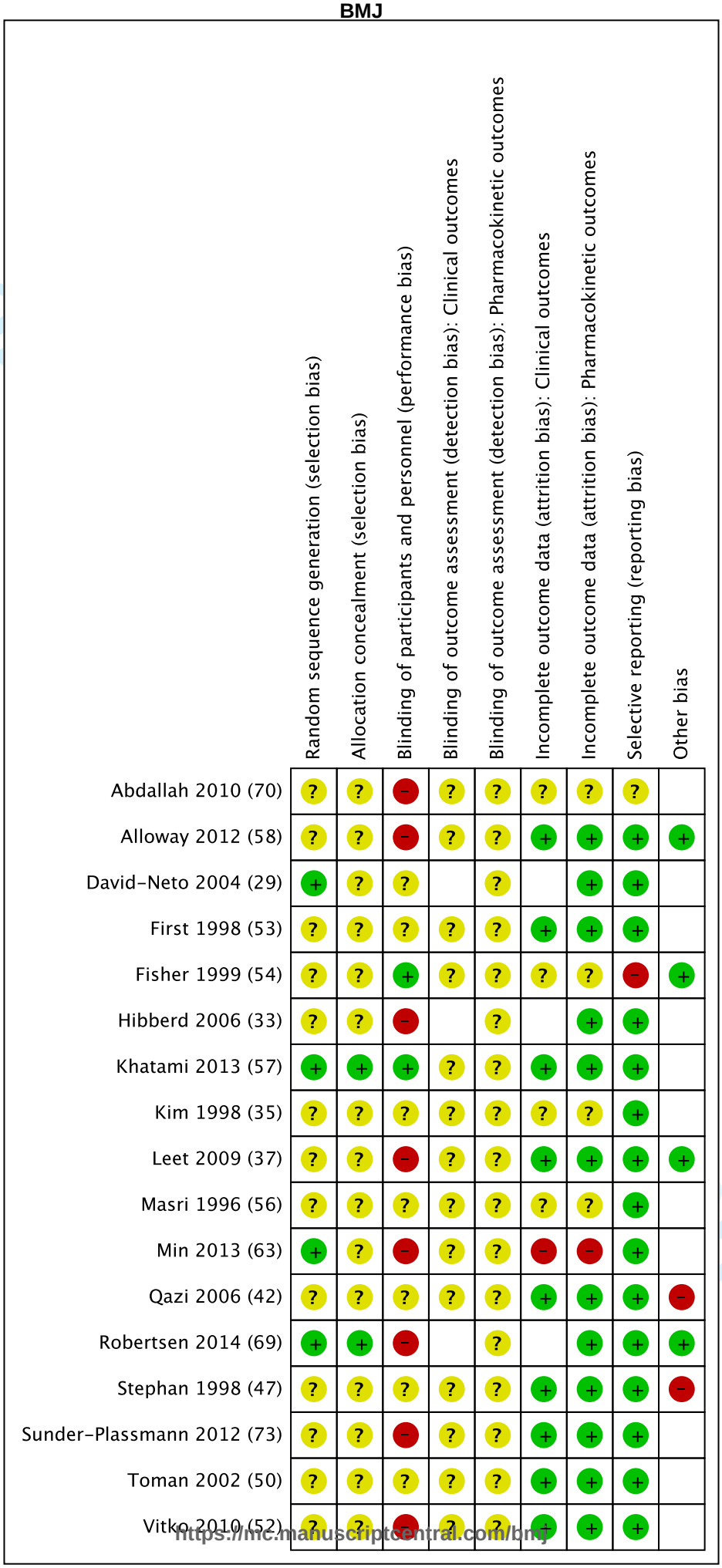
Table 4c: Cellcept clinical outcomes

Outcome	Study, year, organ	Definition of acute rejection	Trial (y/n)	Follow up time	Number of patients analyzed (B/G)	Cellcept	Generic
Acute rejection	Abdallah, 2010, kidney[70]	Not specified	Y	2 years	18 (10/8)	1	1
	Danguilan, 2014, kidney[74]	Not specified	N	6 months	40 (20/20)	3	1
	Rutkowski, 2011, kidney[72]	Clinical manifestations or biopsy	N	6 months	30 (15/15)	2-clinical 1-biopsy	3-clinical 1-biopsy
	Namgoong, 2013, liver[71]	Not specified	N	3 months	47	0	0
Graft loss	Danguilan, 2014, kidney[74]		N	6 months	40 (20/20)	0	0
Death	Sunder-Plassmann, 2012, kidney[73]		Y	112 days	43	0	0
	Abdallah, 2010, kidney[70]		Y	2 years	18 (10/8)	0	0
	Danguilan, 2014, kidney[74]		N	6 months	40 (20/20)	0	1
	Rutkowski, 2011, kidney[72]		N	6 months	30 (15/15)	1	1
Infection	Abdallah, 2010, kidney[70]		Y	2 years	18 (10/8)	14 (episodes)	9 (episodes)
	Danguilan, 2014, kidney[74]		N	6 months	40 (20/20)	3	5
	Rutkowski, 2011, kidney[72]		N	6 months	30 (15/15)	7	7
eGFR (ml/min/1.73m2)	Rutkowski, 2011, kidney[72]		N	6 months	50 (15/15)	58.3	63
Serum creatinine (µmol/L)	Abdallah, 2010, kidney[70]		Y	6 months	18 (10/8)	104.48	121.89
	Abdallah, 2010, kidney[70]		Y	1 month	18 (10/8)	202.55	131.06
	Videla, 2007, kidney[75]		N	Before conversion and 60 days post conversion	Unclear	160 (24.75)	134.37 (15.03)
	Rutkowski, 2011, kidney[72]		N	6 months	30 (15/15)	120.22	114.92

All continuous variables are reported as mean and standard deviation (SD) unless otherwise specified. B/G, B=brand name, G=generic

Supplementary Figure 2: Neoral serum creatinine kidney RCT's





Appendix A

Search Strategy

Database: Embase Classic+Embase <1947 to 2014 March 05>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 Prograf.ti,ab. (602)
2 Cellcept.tw. (2811)
3 Myfortic.tw. (520)
4 Neoral.tw. (5384)
5 gengraf.tw. (160)
6 Rapamune.tw. (1507)
7 mycophenolic acid delayed release.tw. (0)
8 Drugs, Generic/ (12249)
9 generic.tw. (61271)
10 or/1-9 (76022)
11 Tacrolimus/ (63292)
12 tacrolimus.tw. (28711)
13 Mycophenolic Acid/ or mycophenolate mofetil.tw. (27000)
14 Cyclosporine/ (90309)
15 (Cyclosporine or Ciclosporin).tw. (62527)
16 Sirolimus/ (47640)
17 Sirolimus.tw. (14972)
18 brand name$.tw. (3182)
19 or/11-18 (214342)
20 10 and 19 (9511)
21 organ transplantation/ or exp heart transplantation/ or exp kidney transplantation/ or liver transplantation/ or exp lung transplantation/ (421784)
22 ((organ or kidney or renal or heart or cardiac or liver or hepatic or lung or pulmonary) adj2 (transplant$ or graft$)).tw. (366639)
23 21 or 22 (488772)
24 20 and 23 (5265)
25 limit 24 to yr="1980 - 2014" (5259)
26 25 use prmz (1058) Medline

27 prograf.ti,ab. (602)
28 Cellcept.ti,ab. (481)
29 Myfortic.ti,ab. (171)
30 Neoral.ti,ab. (2205)
31 gengraf.ti,ab. (19)
32 Rapamune.ti,ab. (256)
33 mycophenolic acid delayed release.ti,ab. (0)
34 *generic drug/ (6271)
35 generic.tw. (61271)
36 or/27-35 (66509)
37 tacrolimus/ (63292)
38 Tacrolimus.tw. (28711)
39 mycophenolic acid 2 morpholinoethyl ester/ (33579)

40 (mycophenolate mofetil or Mycophenolic acid).tw. (20317)
41 cyclosporin/ (90309)
42 (Cyclosporine or Ciclosporin).tw. (62527)
43 Sirolimus.tw. (14972)
44 brand name$.tw. (3182)
45 or/37-44 (194781)
46 36 and 45 (4869)
47 organ transplantation/ or heart transplantation/ or kidney transplantation/ or liver transplantation/ or lung transplantation/ (401807)
48 ((organ or kidney or renal or heart or cardiac or liver or hepatic or lung or pulmonary) adj2 (transplant$ or graft$)).tw. (366639)
49 47 or 48 (482876)
50 46 and 49 (2430)
51 limit 50 to yr="1980 - 2014" (2424)
52 51 use emczd (1380) Embase

53 26 or 52 (2438)
54 remove duplicates from 53 (1559)

Search was repeated September 4th, 2014

Appendix B

Data abstraction form

Generic Immunosuppressant Review: Data Abstraction Form

Reviewer's Initials: _____ Reference ID Number _____

Lead Author:_____

Journal: _____Year:_____

Language of Publication: 1. English 2. Other (specify)_____

Country(ies) of Study Origin: _____Lebanon___

Immunosuppressants Compared in the Study

Trade Name	Generic (record specific name of generic, ie Tacrobell)
1. Prograf	1. tacrolimus
2. Cellcept	2. mycophenolic acid
3. Neoral	3. cyclosporine (microemulsion)

Patients Included in the Study

Transplant Organ: Lung Liver Kidney Pancreas Heart

Other:_____

New Transplants: yes no

Pediatric Adult

Type of Study

Experimental

1. Randomized parallel group trial
2. Cross over trial
3. Planned before/after (ie investigators switched the drug)
4. Other: _____

Observational

1. Cohort, prospective

2. Cohort, retrospective
3. Before/after prospective
4. Before/after retrospective
5. Other (specify)_____

For before/after studies, was there one to one dose conversion (y/n) _____
Were dose titrations allowed (y/n)_____
Were target drug levels reported in the study?_____

If the study has more than one relevant time period, please record data for both/all

Drug Dosages and Monitoring

If not reported, write n/a

Generic Drug Group

Dose or weight normalized dose (circle one): Mean (SD) or Median (IQR) (circle one)

_____(time period_____) p value_____

_____ (time period_____) p value_____

_____(time period _____) p value_____
(record units)

Number of patients requiring a change in dosage:_____

Dose increased_____ Dose decreased_____

Drug level: How specifically was drug level reported (ie dose normalized level, trough, C2)?_____

Mean (SD) or Median (IQR) (circle one)

_____(time period_____) p value_____

_____ (time period_____) p value_____

_____(time period _____) p value_____
(record units)

Trade Name Drug Group

Dose or weight normalized dose (circle one): Mean (SD) or Median (IQR) (circle one)

_____(time period_____)
_____ (time period_____)
_____(time period _____)
(record units)

Number of patients requiring a change in dosage: _____

Drug level: How specifically was drug level reported?_____

Mean (SD) or Median (IQR) (circle one)_____ (record units)

_____(time period_____)

_____ (time period_____)

_____(time period _____)
(record units)

Outcomes

If more than one relevant time period or type of transplant, record that data above the table and fill in one table for each time period and/or type of transplant

_____

Please report data for all continuous variables as Mean (+/- Standard Deviation)

Variable	Generic group	Trade Name group	P value	Total	Follow up time
Subjects enrolled (n)					
Subjects analyzed (n)					
Men/Women					
Age					
Acute rejection (n)					
Graft loss (n)					
Infection (n)					
Death (n)					

_____

Please report data for all continuous variables as Mean (+/- Standard Deviation)

Variable	Generic	Trade	P	Total	Follow

	group	Name group	value		up time
Subjects enrolled (n)					
Subjects analyzed (n)					
Men/Women					
Age					
Acute rejection (n)*					
Graft loss (n)					
Infection (n)					
Death (n)					

*Record how this was defined (ie biopsy proven)

Renal Function

If more than one relevant time period or type of transplant, record that data above the table and fill in one table for each time period and/or type of transplant

Please report data for all continuous variables as Mean (+/- Standard Deviation)

Variable	Generic group	Trade Name group	Follow up time*	P value
Absolute creatinine (units)				
Absolute eGFR				

Please report data for all continuous variables as Mean (+/- Standard Deviation)

Variable	Generic group	Trade Name group	Follow up time	P value
Absolute creatinine (units)				
Absolute eGFR				

For Bioequivalence Studies Only

Please report data for all continuous variables as Mean (+/- Standard Deviation)

Variable	Generic group	Trade Name group	P value
AUC ( )*			
C_{max}			
T max			
C_0			

*(record time period)

C_{max} mean ratio (90% CI) _____ AUC mean ratio (90% CI) _____

C_0 mean ratio (90% CI) _____

Quality Assessment

For RCT's, fill out the Cochrane Risk of Bias Assessment Tool

Wells et al. criteria for observational studies