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Monitoring the conversion from brand name to generic mycophenolate mofetil in kidney transplant recipients

Monitorização da conversão de micofenolato de mofetil original a genérico em transplantados renais

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ABSTRACT

Generic mycophenolate mofetil (MMF) is a cheaper and possibly equally effective option as the original molecule for maintenance immunosuppression in solid organ transplant recipients. In order to be approved, each generic formulation has to prove bioequivalence to the reference product in healthy volunteers. However, MMF pharmacokinetics may be different between healthy volunteers and transplant recipients. Faced with the introduction of the generic formulation in the pharmacy of their kidney transplant unit, the authors studied and compared the exposure to mycophenolic acid (MPA) before and after the switch in 14 kidney transplant recipients converted to the generic molecule. The exposure to MPA as evaluated by the $AUC_{0\text{-}12h}$ estimated by a limited sample strategy was slightly higher with the generic formulation (40.49 versus 34.96mcg.h/mL, $p = 0.041$). There was no significant variation in the eGFR, haemoglobin and leucocyte count after the switch. Only one of the patients converted to the generic formulation developed *de novo* adverse gastrointestinal effects, which resolved after restart of the original formulation. In conclusion, in our cohort there was no clinically significant variation in the exposure to MPA, kidney graft function or incidence of adverse events with the generic formulation on a short follow-up period.

Key-words: Conversion; generic; immunosuppression; mycophenolate; kidney transplant; tacrolimus.

RESUMO

O micofenolato de mofetil (MMF) genérico é uma alternativa mais barata e possivelmente tão eficaz quanto a molécula original na imunossupressão de manutenção em receptores de transplantes de órgãos sólidos, nomeadamente transplante renal. Para ser aprovada, cada nova formulação genérica tem que

demonstrar bioequivalência ao fármaco original em voluntários saudáveis. No entanto, a farmacocinética do MMF não é necessariamente igual em voluntários saudáveis e receptores de transplantes. Perante a imposição da conversão dos doentes para MMF genérico os autores avaliaram e compararam exposição ao ácido micofenólico (AMF) com o fármaco original e com o genérico em 14 doentes convertidos ao genérico na sua unidade de transplante renal. A exposição ao AMF, avaliada pela AUC_{0-12h} estimada a partir de 3 determinações séricas em tempos pré-definidos, foi ligeiramente mais elevada com a formulação genérica (40.49 versus 34.96mcg.h/mL, p = 0,041). Não se verificou variação significativa da TFGe, hemoglobina nem contagem de leucócitos após a conversão para o fármaco genérico. Apenas um dos doentes convertidos para MMF genérico desenvolveu efeitos adversos do foro gastrointestinal *de novo* que resolveram após reintrodução da molécula original. Em conclusão, na nossa amostra não se verificou variação clinicamente significativa na exposição ao AMF, função do enxerto renal nem na incidência de efeitos adversos com a formulação genérica, a curto prazo.

Palavras-chave: Conversão; genérico; imunossupressão; micofenolato; tacrolimus; transplante renal.

INTRODUCTION

Kidney transplant is the kidney replacement therapy of choice in eligible patients given its survival and quality of life benefits compared with other options. However, among other factors, the associated costs related with the need for lifelong immunosuppression may prevent patient's access to transplant. Therefore, as the patents of the older immunosuppressive medications expire, there has been increasing interest in the use of generic ones given the cost saving potential, namely in kidney transplant.

Mycophenolate is recommended as a first-line antiproliferative agent for maintenance therapy in kidney transplant[1]. Mycophenolic acid is the active metabolite responsible for the immunosuppressive effects.

The registration of generic drugs is based on the demonstration of bioequivalence to the reference one in healthy volunteers. This means that in pharmacokinetic studies the ratio of the geometric means of the generic to reference drug pharmacokinetic parameters of peak concentration and area under the concentration–time curve in one dosing interval (AUC_{0-T}) and AUC_{0-72h} must have a 90% confidence interval within the 80-125% range[2]. However, bioequivalence in healthy volunteers does not guarantee therapeutic equivalence in the kidney transplant population.

A bioequivalence study in kidney transplant recipients has shown that the steady state pharmacokinetics of mycophenolic acid (MPA) after administration of a generic form of mycophenolate mofetil (MMF) or the originator drug is comparable in stable kidney allograft recipients[3]. In this study, the adverse events profile was similar between the two treatment groups. Another study has also shown similar MPA exposure with generic MMF, with no need for dose adjustments and stable graft function[4].

The need for concentration controlled dosing and how MPA exposure is best measured in clinical practice is also a subject of debate[5]. The majority of studies analysing the relationship between MPA exposure and clinical outcomes have shown a good correlation between the full total MPA AUC_{0-12h} and the risk of rejection, at least early after transplantation[6-7]. However, the determination of the full AUC profile requires multiple frequent sampling for determinations of the MPA concentration during a complete dosing interval (usually 12 hours), making it impractical in the clinical setting[5]. Unlike other drugs, MPA concentration at single time points either immediately before or at exact times after dosing have a weak association not only with the full AUC[5], but also with clinical outcomes[6].

Several investigators have shown that a good estimate of MPA AUC_{0-12h} can be obtained by a limited sampling strategy in the first 2 to 4 hours after administration of the drug. Algorithms with acceptable predictive performance have been

proposed for kidney transplant recipients and for regimens that include MMF plus cyclosporine, tacrolimus or sirolimus[8].

Under cost saving constraints, all patients in our kidney transplant unit were switched to a generic MMF formulation. In the present study we aimed to compare the exposure to mycophenolic acid between the original and the generic molecule in a cohort of our patients, to evaluate the efficacy and safety of the conversion to generic MMF.

METHODS

Between May and July 2012, all kidney transplant recipients under maintenance immunosuppression with the original MMF in our unit were converted to the generic molecule, on a 1:1 dose. Generic MMF was always supplied by Generis®. We studied the first 14 patients to be converted who were, at least, 12 months post-transplantation, with stable kidney graft function (no increase in serum creatinine from baseline of more than 0.3mg/dL in the previous 3 months) and willing to participate in the study. Each of these 14 patients underwent blood sampling in the unit at two time points: the first while taking the original molecule and the second 3 weeks after conversion to the generic MMF.

The protocol for determination of the MPA $AUC_{0\text{-}12h}$ was the following: blood samples for MPA analysis were collected immediately before (C_{0h}) administration of the drug and at 30 minutes ($C_{0.5h}$) and 2 hours (C_{2h}) after administration. These samples were immediately centrifuged, frozen and stored at -20 ºC until analysis. MPA plasma concentrations were measured using an enzymatic method. The $AUC_{0\text{-}12h}$ was calculated using the following formula[9]: $AUC_{0\text{-}12h} = 7.75 + 6.49C_{0h} + 0.76C_{0.5h} + 2.43C_{2h}$.

We collected patient data concerning demographics, graft function as estimated by de 4 variable Modification of Diet in Renal Disease equation (eGFR), through levels of calcineurin or mTOR inhibitors, haemoglobin and leucocyte count immediately before and 3 weeks after conversion. Any adverse events during the period of the study were registered. Additionally, an estimate on the costs related to MMF prescription was obtained before and after the conversion. The statistical analysis comparing the values before and after the conversion was done using a paired T-test.

RESULTS

All 14 patients completed the protocol for determination of MPA $AUC_{0\text{-}12h}$ before and after the conversion. A total of 28 determinations of $AUC_{0\text{-}12h}$ were obtained with the original and the generic molecule. There was no change in the MMF dose for each patient during the study (500mg to 2g/day). The baseline characteristics of the patients are presented in Table I. There was no variation of the doses or levels of the calcineurin and mTOR inhibitor during the study. There was also no change in the additional medication. The results of the mycophenolic acid determinations are shown in Table II. There was no significant variation in the eGFR, haemoglobin or leucocyte count after the switch (Table III). Only one of the patients converted to generic MMF developed *de novo* adverse gastrointestinal effects, which resolved after restart of the original formulation. In this patient, although there was no significant variation of the $AUC_{0\text{-}12h}$ (69 mcg.h/mL with both formulations), $C_{0.5h}$ was significantly higher with the generic formulation (24 versus 11.8mcg/mL).

The costs related to MMF prescription in our unit are presented in Table IV, showing a reduction both in cost per pill and in global costs.

Table I

Baseline characteristics of the patients studied

Age	56 (min 25; max 73)
Male	7 (50%)
Caucasian	14 (100%)
Median time post kidney transplant (years)	7 (min 1; max 16)
eGFR (mL/min/1.73m²)	61(± 24.5)
Additional immunosuppression	
Prednisolone	14 (100%)
Tacrolimus	4 (28%)
Cyclosporine	6 (43%)
Sirolimus	2 (14%)
Everolimus	2 (14%)

Table II

Plasma concentrations and exposure to mycophenolic acid with the original and generic MMF

	Original MMF	Generic MMF	Δ (g-o)	p
$AUC_{0\text{-}12h}$ (mcg.h/mL)	34.93 (± 14.18)	40.49 (± 12.46)	5.57 (± 9.21)	0.041
C_{0h} (mcg/mL)	1.55 (± 0.80)	2.00 (± 0.80)	0.45 (± 1.04)	0.127
$C_{0.5h}$ (mcg/mL)	8.23 (± 5.24)	10.89 (± 5.89)	2.67 (± 5.04)	0.069
C_{2h} (mcg/mL)	4.47 (± 3.99)	4.72 (± 2.06)	0.25 (± 3.17)	0.772

Table III

Variation of the eGFR, haemoglobin and leucocyte count

	Original MMF	Generic MMF	Δ (g-o)	p
eGFR (mL/min/1.73m^2)	61 (± 24.5)	57 (±20)	-4.1 (± 6.2)	0.109
Haemoglobin (g/dL)	12.0 (± 1.5)	11.9 (± 1.2)	-0.1 (± 0.9)	0.420
Leucocyte count (x10^9/L)	6.69 (± 1.41)	6.96 (± 1.92)	+0.01(± 1.28)	0.739

Table IV

Costs related to MMF prescription

	Before conversion (2011)	After conversion (2013)
Costs per 500mg pill (€)	2.05	0.24
Annual global costs (€)	259.495	38.001

DISCUSSION

We have undertaken a small prospective study comparing pharmacokinetic variables and graft function before and after conversion to a generic formulation of MMF in selected stable kidney transplant recipients at a single centre.

An association between MPA exposure, especially when evaluated by either limited sampling or full $AUC_{0\text{-}12h}$, and the risk of acute rejection has been shown in observational and randomized trials[5,7-9]. According to their results, a therapeutic window of 30 to 60 mcg.h/mL has been proposed for patients with low to intermediate immunologic risk and who are on calcineurin inhibitors based therapy[5]. It is worth mentioning that these trials enrolled patients in the first 3 months post-transplantation. Data including patients in a later post-transplantation period or under calcineurin inhibitors minimization/withdrawal protocols are lacking.

Our data showed a slightly higher exposure to mycophenolic acid with the generic formulation compared to the original one, which was statistically significant. Nevertheless, most patients showed an MPA exposure within the target range with both MMF formulations, suggesting that the difference observed has no clinical implications. This is supported by the absence of significant variation of the graft function measured by eGFR (MDRD) or haematologic parameters (haemoglobin and leucocyte count) during the study period.

Only one of the patients that were switched to the generic formulation developed *de novo* gastrointestinal complaints. After restart of the original formulation the symptoms subsided. Contradictory results have been reported on the relationship between MPA exposure and adverse events. Although larger studies have shown no correlation[5,7-9], between MPA predose trough concentration or $AUC_{0\text{-}12h}$ and MMF related adverse events, one study has reported an association between higher MPA concentrations at 30 minutes after MMF dosing and adverse events[10]. The only patient in our population that developed an adverse reaction attributable to generic MMF, namely gastrointestinal intolerance, showed a higher MPA concentration at 30 minutes with the generic formulation, with the same $AUC_{0\text{-}12h}$.

From an economical point of view, there were considerable cost savings with the introduction of

the generic formulation. The conversion allowed an 88% reduction on the cost per 500mg pill and an 85% reduction on the global annual costs with MMF prescription in our centre.

This study has several limitations, namely the small number of patients enrolled, the short follow-up period and the fact that this protocol for determination of the exposure to MPA is impractical in our daily practice. The question remains on whether this pharmacokinetic overlap in kidney transplant recipients translates into therapeutic equivalence. Larger studies with longer follow-up are needed to assess the long-term effectiveness and safety of the generic drug.

CONCLUSION

In our cohort, there was a statistically significant increase in the exposure to MPA with the generic formulation of MMF. Nevertheless, most patients showed an MPA exposure within the target range with both MMF formulations and stable graft function and haematologic parameters after the switch. Only one patient had to suspend generic MMF because of *de novo* adverse gastrointestinal symptoms. The conversion to generic MMF resulted in significant cost-savings. Despite the small number of patients included in the study, our data suggest that the switch to generic MMF may be safe and effective in stable kidney transplant recipients, at least on the short term. Additional studies to evaluate the long-term safety and cost-effectiveness of generic MMF conversion are warranted.

***Conflict of interest statement*:** None declared.

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