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# Calcineurin Inhibitor-Free Maintenance Therapy After Liver Transplantation I: Mycophenolate Mofetil and Renal Function

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## Abstract

***It has been widely reported that continued therapy with calcineurin inhibitors can cause an up to fourfold increase in morbidity and mortality in long-term liver transplant patients due to the development of chronic renal failure as well as neurotoxicity, arterial hypertension, hyperglycemia, hyperlipidemia, and increased risk of* de novo *tumors.***

***These side effects have led to the development of other treatment options that allow these drugs to be minimized or withdrawn.***

***Mycophenolate mofetil is one of the immunosuppressive drugs that has made it possible to discontinue calcineurin inhibitors in liver transplantation. Its side effects are mainly related to the gastrointestinal tract and bone marrow. Furthermore, it lacks nephrotoxic, metabolic, and neurological effects.***

***In the last decade numerous papers have been published, based on the study of liver transplant patients treated with mycophenolate mofetil monotherapy in different countries. They analyzed the safety and efficacy of this therapy, focusing primarily on its effect on chronic renal failure, metabolic complications, and incidence of graft rejection.***

***After reviewing all these works we know that mycophenolate mofetil therapy reduces calcineurin inhibitor-induced renal damage by allowing minimization of the doses of these drugs and their subsequent withdrawal. It has been widely shown that the switch to mycophenolate mofetil monotherapy improves and maintains stable serum creatinine and creatinine clearance values as well as improving hypertension and hyperlipidemia in the long term.***

***On the other hand, most studies found that the improvement in the clinical variables analyzed occurred in the first three months after conversion, so it is clear that a large part of the renal damage and other side effects are induced by the calcineurin inhibitors because it is in that period when the largest reduction is made in the dose of these drugs until their complete withdrawal.***

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***However, these variables continue to improve after withdrawal so we should consider that the long-term effect of mycophenolate mofetil monotherapy is beneficial.***
***The disparity in the incidence of rejection in the different studies presented should be highlighted, but nevertheless, they all have in common the fact that rejections occurred in the majority of cases in the first three months after the start of conversion.***
***The side effects of mycophenolate mofetil, such as gastrointestinal complications and hematological problems, were reversed in most cases simply by a temporary reduction in the drug dose, so we can consider that the benefits outweigh the risks in this regard.***
***Based on all the studies analyzed, we can infer that the ideal patient for long-term withdrawal of calcineurin inhibitors is a patient who clearly has calcineurin inhibitor-induced chronic renal failure and is not on dialysis, who has not suffered severe acute rejection episodes in the last year, and who has not shown intolerance to mycophenolate mofetil previously.*** **(Trends in Transplant. 2010;4:117-28)**

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## Key words

***Calcineurin inhibitor. Chronic renal failure. Mycophenolate mofetil. Monotherapy. Acute rejection.***

## Introduction

In 1980, a new class of immunosuppressive agents called calcineurin inhibitors (CNI) was developed. This allowed the safety of the immunosuppressive regimens used in liver transplantation (LTx) to be improved, since the use of these CNI provided a considerable reduction in the risk of suffering rejection and also increased short-term survival[1]. As a result, CNI, either tacrolimus or cyclosporine, are a key element in all baseline immunosuppression therapies.

However, it has been widely reported that continued use of these drugs can cause up to a fourfold increase in morbidity and mortality in long-term liver transplant patients due to the development of chronic renal failure (CRF), as well as neurotoxicity, arterial hypertension, hyperglycemia, hyperlipidemia and increased risk of *de novo* tumors[2-4].

The incidence of CRF at five years post-transplantation is high, and although its origin is multifactorial, in over 70% of cases renal damage is directly related to the CNI dose.

It is also known that hemodialysis and even renal transplantation is required in nearly 10% of patients with end-stage renal disease; this was analyzed in detail in a study of 834 patients with 13 years of post-LTx follow-up[5].

The nephrotoxic impact, among others, caused by these CNI has led to the development of other treatment options that allow these drugs to be minimized or withdrawn, mainly in the maintenance phase, and thus reduce the incidence and prevalence of CRF.

One of the immunosuppressive drugs that has made it possible to discontinue these CNI in LTx is mycophenolate mofetil (MMF). This is a semi-synthetic ester of mycophenolic acid, which acts as a potent inhibitor of the proliferation of B and T lymphocytes[6]. Its side effects are mainly related to the gastrointestinal tract (diarrhea, nausea, abdominal pain, etc.) and bone marrow (leukopenia,

thrombopenia and anemia). Furthermore, it lacks nephrotoxic, metabolic, and neurological effects.

The first steps towards MMF monotherapy were made in studies where MMF was introduced due to CNI-induced renal toxicity, with the consequent reduction in the doses of these CNI[7-9].

Pfitzmann, et al. conducted a study in a series of 101 patients receiving both tacrolimus and cyclosporine as CNI, who developed CNI-induced CRF and were treated by reducing the dose of CNI and adding MMF to treatment.

The results obtained were a reduction in serum creatinine (SCr 0.4 mg/dl; $p < 0.001$) after a mean follow-up of 40 months. Of these 101 patients, 56 also had graft dysfunction, and it was found that they also showed improvements versus baseline in bilirubin ($p < 0.019$) and alkaline phosphatase ($p < 0.002$) from 2.9 ± 0.8 to 1.3 ± 0.3 mg/dl and from 321 ± 41 to 208 ± 18 UI/l, respectively. It should be noted that there were two patient deaths from sepsis and renal dysfunction and that MMF therapy was associated with a high rate of side effects (37 patients): gastrointestinal (n = 26), bone marrow toxicity (n = 9), and infections (n = 2). However, the rate of acute rejection did not increase with respect to standard full-dose CNI therapy[7].

On the other hand, Cantarovich, et al. analyzed 19 LTx patients receiving cyclosporine who developed posttransplant renal dysfunction induced by this drug. They reported a clear improvement in renal function evaluation parameters with the introduction of MMF and reduction in cyclosporine dose, since mean creatinine clearance (CrCl) increased by 18 ml/min ($p < 0.02$) and mean glomerular filtration rate by 24 ml/min ($p = 0.002$); in addition, 71% of patients who were receiving antihypertensive therapy were able to discontinue it. However, the rate of acute rejection as a result of the treatment change was high (29%)[8].

A third study on CNI dose reduction for CRF by the introduction of MMF was published by Beckebaum, et al.[9]. It was randomized study (2:1) in which all patients were diagnosed with CRF and it compared the changes in different clinical variables (mainly related to renal function) between the control group, which continued with normal doses of CNI monotherapy, versus the case group in which MMF was introduced and CNI doses were minimized.

After three months of follow-up, significant improvements were observed in the group receiving low-dose CNI but not in the group receiving standard therapy.

Mean values of SCr decreased from 1.88 ± 0.36 to 1.58 ± 0.33 mg/dl ($p < 0.001$) and CrCl increased from 51.4 ± 10.8 to 61.6 ± 14.1 ml/min ($p < 0.001$).

The authors also suggested that despite the fact that the mean time from LTx to the start of treatment was 5.6 ± 3.6 years, CNI-induced renal damage appeared to be partially reversible.

They also found that the group of patients with low-dose CNI and MMF improved their lipid profile and blood pressures at three months, and more importantly, they found that transaminases were significantly reduced.

The efficacy of MMF therapy in improving CRF and its safety on liver graft function was thus demonstrated in patients with CNI-induced toxicity.

## Mycophenolate mofetil monotherapy

Since numerous studies have shown that use of MMF allows CNI doses to be minimized

safely and effectively in LTx, the next step to achieve CNI-free therapies would be to consider immunosuppressive regimens without them[7-9].

A long-term treatment option could be MMF monotherapy, as this would largely avoid the side effects of CNI, mainly chronic renal disease, arterial hypertension, hyperlipidemia, hyperglycemia, and *de novo* tumors.

In the last decade, a considerable number of studies have been generated on this topic, where it can be seen that there are some authors with results favorable to MMF monotherapy as a safe, long-term treatment in LTx, while others found that the risk was greater than the benefit (Table 1).

One of the first published studies on this problem was that of Herrero, et al., who attempted conversion to MMF monotherapy in a group of 11 patients with CRF (SCr > 1.5 mg/dl), stable liver function, and no episodes of acute rejection within one year before the treatment change. All patients were started on full doses of MMF (2 g/day), simultaneously slowly reducing the dose of cyclosporine. After a mean time of 15 months, seven patients had achieved CNI-free therapy with MMF, with SCr decreasing from 2.22 ± 0.13 mg/dl at baseline to 1.90 ± 0.19 mg/dl and CrCl increasing from 38.16 ± 5.60 to 47.01 ± 6.76 ml/min (p = 0.005). In addition, these patients experienced an improvement in control of arterial hypertension, with a reduction in the number of antihypertensive drugs, as only two of seven patients required antihypertensive treatment at the end of follow-up.

The side effects observed were those expected for MMF, and in six patients the dose had to be reduced due to mild anemia.

Complete conversion to MMF was not achieved in four of 11 patients as two patients were switched to tacrolimus due to acute rejection (18%) and another two continued with low-dose cyclosporine.

The results seemed quite promising since the patients considerably improved renal function and tolerance of MMF was good. The incidence of rejection was also acceptable since it was easily reversed and no graft loss or patient death occurred[10].

However, several years later two studies were published with the same objectives of conversion to MMF monotherapy to minimize CRF from CNI, with very unpromising results since despite improving renal function the incidence of acute rejection increased alarmingly[11,12].

The first study was conducted by Stewart, et al. and consisted of a case-control study. The study enrolled patients with CRF who in some cases also had associated arterial hypertension. The initially estimated number of patients was 18, of which nine would be the control group (treated with azathioprine and CNI) and the case group would be composed of another nine patients treated with MMF monotherapy with slow CNI tapering.

However, when five patients had already been enrolled, the study had to be discontinued because of the high rate of severe organ rejection (two chronic rejections and one acute rejection). The consequence was that two of the five patients had to be retransplanted soon (mean 4 months) after starting the study and one patient received steroid therapy for acute rejection. Therefore, the risk posed by this treatment was unacceptable, independently of whether it improved renal function parameters[11].

Schlitt, et al. obtained similar results to the previous group. They designed a case-control study with 28 patients; 14 patients continued with standard CNI therapy and the other 14 patients in the case group were

converted to MMF monotherapy. Eight patients from the latter group continued with steroids combined with MMF, so only six were treated with MMF monotherapy. Of these, three patients suffered recurrence of hepatitis C virus accompanied by mild rejection, one patient stopped treatment due to intolerable diarrhea, and the two remaining patients also developed moderate acute cellular rejection[12].

This discrepancy of results between the different groups led to the generation of more controlled studies with larger numbers of patients in which it was attempted to analyze long-term MMF monotherapy, taking special care due to the high risk of rejection and consequent organ loss. Fortunately, the studies that were published in successive years presented results of series with rejection incidence rates not superior, in the majority of cases, to 10-15%[13-15,17-20].

In 2003, the data from Raimondo, et al. were published. They conducted a study with 45 patients, all with CRF associated with CNI; one of the treatment arms was formed by patients on MMF monotherapy (n = 16) in doses of 2 g/day. The mean follow-up period was 24 months, SCr values improved in five of eight patients who completed the two years of treatment from 1.79 mg/dl (1.20-3.36) at baseline to 1.22 mg/dl (97-2.15) at the end of the study[13].

Four patients died from causes not directly related to immunosuppression with MMF monotherapy. Only one case of acute rejection (6%) was diagnosed in the 16 patients included, and interestingly, it was the only patient who had had rejection prior to inclusion in the study. The authors concluded that the presence of rejection episodes could be a risk factor to be considered when deciding on monotherapy.

This may be what occurred in the studies by Stewart and Schlitt, as it is not defined if the patients randomized in their studies had previously suffered any episode of acute rejection. Perhaps this, among other factors, explains their high rate of rejection.

Therefore, the fact that MMF monotherapy is clearly beneficial in improving renal function in patients who only have CNI nephrotoxicity is unquestionable, even if therapy is started several years after LTx, because although in many cases normalized values of SCr or CrCl are not achieved, an improvement in renal function is obtained.

One year later, three new studies were published that help to improve our learning about CNI-free therapy with MMF monotherapy through the experience of different centers performing LTx[14-16].

The first study carried out by Koch, et al. included 32 patients with CRF who were split into two groups according to time since LTx. Thus, one group was formed by patients less than six months posttransplantation (n = 14) and the other by patients who were transplanted more than six months previously (n = 18)[14].

In 88% of patients, there was a significant reduction in SCr values from 2.63 ± 0.39 to 1.74 ± 0.34 mg/dl. Furthermore, a higher proportion of patients normalized SCr values in the group with early MMF conversion: 64% versus 22% in the second group. As a negative point, it should be noted that three patients had to be entered in hemodialysis, but it should be clarified that none of them had diabetic nephropathy.

As in previous studies, the rejection rate was minimal at 6% (2/32 patients), and may have been because patients with previous episodes of severe rejection were not excluded. Special mention should be made of the fact that five patients died in this study: two from cardiovascular problems, one from *de novo*

**Table 1. Studies about treatment in monotherapy with MMF in LTx with CRF induced by CNIs**

| Author | Year of publication, city | Type of study | Number of patients | Follow-up from LTx to conversion (months) | Indication for conversion | Type of CNI | MMF daily dose (grams) |
|---|---|---|---|---|---|---|---|
| Herrero, et al.[10] | 1999, Pamplona | Prospective | 11 | 32 | CRF | CsA | 2 |
| Stewart, et al.[11] | 2001, Newcastle | Prospective randomized case-control | 5 | Not specified | CRF Hypertension | CsA | 2 |
| Schlitt, et al.[12] | 2001, Hannover | Prospective randomized case-control | 14 | 76 | CRF | CsA/Tac | 2 |
| Raimondo, et al.[13] | 2003, London | Retrospective | 16 | 45 | CRF | CsA/Tac | 2 |
| Moreno-Planas, et al.[15] | 2004, Madrid | Prospective | 50 | 81 | CRF Hypertension | CsA/Tac | 2 |
| Koch, et al.[14] | 2004, Innsbruck | Prospective | 32 | 25.6 | CRF | CsA/Tac | 2 |
| Fairbanks and Thuluvath[16] | 2004, Baltimore | Retrospective | 13 | 69 | CRF Histoplasmosis | CsA/Tac | Not specified |
| Pierini, et al.[17] | 2005, Turin | Retrospective | 32 | 50 | CRF *De novo* tumor | CsA/Tac | 1.5 |
| Orlando, et al.[18] | 2007, Rome | Prospective | 42 | 70.5 | CRF Hypertension Hyperlipidemia Hyperuricemia Gingival hyperplasia | CsA/Tac | 1.5 |
| Barrera-Pulido, et al.[20] | 2008, Seville | Prospective | 31 | 87 | CRF | CsA/Tac | 2 |
| Ko, et al.[19] | 2008, Vancouver | Retrospective | 15 | 135 | CRF | CsA/Tac | 2 |
| Kamphues, et al.[21] | 2009, Berlin | Retrospective | 123 | 91 | CRF | CsA/Tac | 2 |

LTx: liver transplantation; CNI: calcineurin inhibitor; MMF: mycophenolate mofetil; CRF: chronic renal failure; CsA: cyclosporin A; Tac: tacrolimus; HCV: hepatitis C virus; HCC: hepatocellular carcinoma.

| Patients on MMF monotherapy at the end of the study | Acute rejection | Follow-up time (months) | Adverse effects of MMF | Patients who developed intolerance to MMF | Improvement of renal function | Improvement of arterial hypertension | Death |
|---|---|---|---|---|---|---|---|
| 6/11 (55%) | 2/11 (18%) | 15 | 6/11 (55%) | 0/11 (0%) | 10/11 (91%) | 6/7 (86%) | 0/11 (0%) |
| 2/5 (40%) | 3/5(60%) | 0 | – | – | – | – | 0/5 (0%) |
| 6/14 (42.8%) | 5/14 (36%) | 6 | 8/14 (57%) | 0/14 (0%) | 11/14 (79%) | 14/14 (100%) | 0/14 (0%) |
| 8/16 (50%) | 1/16 (6%) | 33 | 2/16 (13%) | 0/16 (0%) | 5/8 (63%) | – | 4/16 (25%): 3 recurrences, 1 alcoholic, 1 HCV and 1 HCC. 1 *de novo* tumor |
| 39/50 (78%) | 5/50 (10%) | 18 | 26/50 (52%) | 3/50 (6%) | 32/40 (80%) | 24/32 (75%) | 2/50 (4%): alcoholic recurrence |
| 9/32 (28%) | 2/32 (6%) | 57 | 17/32 (53%) | 0/32 (0%) | 8/9 (88%) | – | 5/32 (16%): 2 cardiovascular problem, 1 *de novo* neoplasm, 1 tumor recurrence, 1 sepsis |
| 11/13 (85%) | 3/13 (23%) | 22 | Minimal | 0/13 (0%) | No significant improvement | – | 3/13 (23%): 2 severe liver failure due to alcoholic recurrence, 1 HCV recurrence |
| 32/32 (100%) | 1/32 (3%) | 17.9 | 9/32 (28%) | 0/32 (0%) | Significant improvement (% not specified) | – | 0/32 (0%) |
| 41/42 (98%) | 9/42 (21%) | 24 | 7/42 (17%) | 0/42 (0%) | 31/36 (89%) | 4/5 (80%) | 0/42 (0%) |
| 31/31 (100%) | 0/31 (0%) | 12 | 5/31 (16%) | 0/31 (0%) | 21/31 (67.7%) | – | 0/31 (0%) |
| 12/15 (80%) | 1/15 (7%) | 10 | 5/15 (33%) | 3/15 (20%) | 13/15 (87%) | – | 0/15 (0%) |
| 123/123 (100%) | 0/123 (0%) | 12 | Minimal | 0/123 (0%) | Significant improvement (% not specified) | – | 0/123 (0%) |

pancreatic neoplasm, one from recurrence of cholangiocarcinoma, and one from sepsis due to cholangitis.

The second study, published in 2004 with optimum results in terms of rejection with MMF monotherapy, was that of Moreno, et al.[15]. Fifty patients were converted to this treatment because of CNI-associated toxicity: 45 had CRF (in 11 associated with arterial hypertension) and five had hypertension as the only complication.

At 18 months, 78% of patients were no longer receiving CNI as immunosuppressive treatment. The SCr values decreased from 1.81 to 1.49 mg/dl ($p < 0.0001$), CrCl increased from 44.7 to 55.1 ml/min ($p < 0.0001$); therefore, 80% of patients achieved an improvement in renal function.

An acute rejection rate seen was 10% (five patients). Side effects occurred in 52% of patients and consisted mainly of asthenia, diarrhea, and viral infections.

In conclusion, this study reinforces the idea that MMF monotherapy late after LTx is well tolerated and safe and clearly improves CNI-induced CRF and hypertension.

In contrast to the two previous studies is a third retrospective study published in the same year and including 13 patients with CRF[16]. The results obtained for the incidence of rejection in this series were rather more dangerous at 28% (three of the 13 patients included). In addition to these three patients, two died due to rejection and another had to be re-transplanted.

With regard to renal function, even though conversion to MMF was indicated for CRF, MMF therapy was not effective in some cases as four patients required dialysis. However, in those not requiring dialysis, SCr values were decreased from 2.51 ± 1.12 to 1.85 ± 0.58 mg/dl ($p = 0.01$), as has been widely reported in the studies we are analyzing.

These data led to the use of MMF monotherapy being questioned again as this study attributed a 19% risk of death to treatment with MMF alone.

The results lead us to think that special care should be taken when selecting patients and the time of conversion to be sure that the benefit outweighs the risk associated with the use of this therapy.

Fortunately, in the previous year the results of the study by Italian group from Turin were published in which they retrospectively analyzed their experience with MMF monotherapy[17].

Conversion to MMF was at a median of 50 months post-LTx in 32 patients (for CRF in 30 and *de novo* tumors in two), and over 90% were receiving cyclosporine as the CNI. Unlike the regimens of the other centers, the mean dose of MMF administered was 1.5 g/day.

Once more, the positive effect of MMF monotherapy on renal function was confirmed, with baseline SCr values decreasing from 2.02 to 1.7 mg/dl ($p = 0.0001$). The rejection rate was also minimal as only one case was diagnosed among the 32 patients (3%).

Obviously, the treatment change was not free of side effects, as was also reported by other authors, such as diarrhea (12.5%) and leukopenia (15.6%).

Two years later, Orlando, et al. published their experience with 42 patients[18]. In this case, they attempted to optimize MMF monotherapy in order to avoid the high incidence of MMF-related side effects. Therefore, they converted all patients to MMF therapy at initial doses of 1.5 g/day instead of 2 g/day (standard therapy).

Another novel feature of this study is the expansion of the indications for monotherapy: only for CRF (n = 22), CRF associated with hyperlipidemia (n = 10), hypercholesterolemia (n = 4), CRF associated with hyperlipidemia and hypertension (n = 2), hypercholesterolemia associated with hypertension (n = 1) and gingival hyperplasia (n = 1).

Calcineurin inhibitors were reduced by 25% monthly until permanent withdrawal (mean of 4.5 months).

Of the 35 patients included for CRF, 31 improved their renal function at one year, as SCr decreased from 1.8 ± 0.4 to 1.56 ± 0.4 mg/dl and CrCl increased from 47.8 ± 10.4 to 57.6 ± 17 ml/min ($p < 0.05$). They also obtained considerable improvements in patients converted for hyperlipidemia, as triglycerides decreased in 14 of 17 patients (82%) and cholesterol in 12 of 13 patients (92%) at one year and the reductions were maintained at two years of follow-up. In addition, three of the five patients who were being treated with statins were able to discontinue this treatment.

Conversion also allowed blood pressure to be controlled and improved (80%), as two of the four patients who were receiving antihypertensive treatment were able to discontinue it at five and seven months after conversion to MMF.

However, it should be noted that there was a high incidence of suspected rejection episodes, all within the first six months after conversion, since they occurred in nine of the 42 patients studied (21%). In any case, the authors state that this does not represent an important clinical problem as no graft loss or untreatable rejection occurred. In fact, all rejections were reversed by increasing the MMF dose to 2 g/day and/or optimizing the CNI dose.

A very positive finding of this study was the considerable reduction in side effects related to MMF. Only seven of 42 patients (16%) experienced any side effect: nausea and vomiting in two patients, asthenia in two, leuko-thrombopenia in three, and herpes zoster skin infection in one patient. It should be stressed that no case required treatment discontinuation.

This article demonstrated the efficacy of MMF monotherapy in doses of 1.5 g/day to improve renal function, dyslipidemia, and hypertension as well as its relative safety. However, the authors stress that it was at three months from the start of conversion when a frank improvement was observed in most patients, that is when CNI had been reduced by 75%. Therefore, they propose the idea that perhaps it is not necessary to completely withdraw the CNI, but rather to reduce them to a minimum and simultaneously administer MMF in doses of 1.5 g/day, with the consequent reduction in undesirable effects.

Subsequently, in 2008, the experiences of another two centers were published who treated their long-term liver transplant patients with CNI-free therapies based on MMF[19,20].

The first study conducted by Ko, et al. in Vancouver has a clear limitation because the sample size is small (18 patients) and the median follow-up time is very short, in addition to being done retrospectively[19].

No dialysis patients were included who had suffered a rejection episode in the year previous to conversion, nor patients who had CRF induced by any other cause than CNI toxicity.

Nevertheless, the results obtained provide quite a lot of information since they analyzed the effect of conversion to MMF monotherapy at three and six months post conversion and, like other authors, concluded that a significant improvement occurred in the different clinical variables during the

first three months, with no differences between the third and sixth month. Median SCr values at baseline were 1.44 mg/dl: 1.29 mg/dl at three months (p = 0.001) and 1.39 mg/dl at six months (p = 0.008).

Side effects were those usually seen with MMF. Three patients experienced gastrointestinal intolerance (one had to discontinue MMF), one had anemia (also discontinued MMF), and one had atrial fibrillation (despite being unrelated to MMF, it was discontinued as a precaution).

In terms of graft function, only one patient experienced elevated liver enzymes, which was considered acute rejection (6.7%), although biopsy was not performed, and was treated by adding sirolimus to immunosuppressive treatment.

The second published series was carried out prospectively at our institution, Virgen del Rocio University Hospital in Seville[20]. Like the other groups, we made the switch to MMF monotherapy in patients with CNI-induced CRF, slowly reducing the CNI dose by 25% every 2-3 months up to complete withdrawal. Unlike the experiences of other authors, our patients were not on CNI monotherapy and subsequently switched to MMF, but were already receiving this dual therapy previously.

Like the previous authors, we excluded from the study patients who were on dialysis, patients with CRF not induced by CNI, patients with chronic rejection or any episode of acute rejection in the last year, and finally we excluded patients who were receiving dual immunosuppressive therapy (CNI plus MMF) and who had shown intolerance to MMF in full doses (2 g/day).

The mean time from LTx to monotherapy was 87 months (range 14-186 months) and the minimum follow-up time post conversion was 12 months.

The different clinical variables analyzed improved significantly between three and six months posttransplantation and remained stable at 12 months. Thus, mean SCr values were reduced from 1.63 ± 0.47 mg/dl at baseline to 1.49 ± 0.33 mg/dl at six months ($p < 0.05$).

No significant side effects were recorded, although we had to change the dose of MMF in three cases due to gastrointestinal disturbances and reduce the dose in two patients because of mild leukopenia.

With regard to graft function, there was no case of graft loss or rejection.

Therefore, we also concluded that this therapy based on MMF is effective and safe provided that patients are carefully selected and closely monitored. Nevertheless, we must continue longer-term evaluation of these patients because most currently continue on this immunosuppressive therapy.

The last study published in 2009 on CNI-free therapy based on MMF was conducted by the group of Kamphues, et al. in Berlin[21]. It is a retrospective analysis of 123 liver transplant patients in whom MMF monotherapy was carried out effectively for CNI-induced CRF. They only included patients who completed conversion to MMF and did not suffer acute rejection episodes in the first three months after conversion from CNI to MMF. They present and analyze the experience of other groups in terms of the incidence of rejection and the results they obtained showed that most rejections occur at three months after the switch to monotherapy[11,12,18]; therefore, if they eliminate this group of patients from the start they can evaluate the real effect of treatment with MMF alone.

They also included another novelty with respect to previous studies, since in 59 of the 123 patients they performed biopsies before

and after conversion (although not at a specific time pre- and post-LTx) to evaluate the histopathological changes that might be caused by the drug in the organ, including acute rejection, chronic rejection, fibrosis, steatosis, etc.

The results obtained were very positive as no episode of chronic or acute rejection was recorded in 12 months of follow-up post conversion. Fibrosis was observed in eight of 59 patients (13%), a lower grade of fibrosis was detected in 14 patients (24%), and fibrosis remained stable versus the pre conversion MMF biopsy in 37 patients (63%).

On the other hand, an increase in liver fat content was detected in 24 of the 59 patients (41%). In addition, mean fat content of all patients analyzed by biopsy (n = 59) was significantly increased from 9.8 ± 15.9% before conversion to MMF monotherapy to 16.1 ± 21.0% after conversion ($p < 0.05$).

The authors were unable to explain this pathophysiological effect of increased fat in the liver, and were also unable to compare their experience with that of other groups because this was the first study in which biopsy was done before and after the start of treatment.

As this effect of MMF on liver tissue has not been reported by other authors, it would be of great utility to design a prospective study with protocol biopsies before and after conversion to see if the results are repeated in patients from other groups; this would help us to further advance our knowledge on the safety of this CNI-free therapy.

In their study, as in the rest of the previously mentioned studies, renal function was significantly improved from baseline SCr values of 1.54 ± 0.59 to 1.47 ± 0.61 mg/dl at 12 months.

## Conclusions

After reviewing all the above studies, we know that MMF therapy reduces CNI-induced renal damage by allowing minimization of the doses of these drugs and their subsequent withdrawal. It has been widely shown that the switch to MMF monotherapy improves and maintains stable SCr and CrCl values as well as improving hypertension and hyperlipidemia in the long term.

On the other hand, most studies found that the improvement in the clinical variables analyzed occurred in the first three months after conversion, so it is clear that a large part of the renal damage and other side effects are induced by the CNI because it is in that period when the largest reduction is made in the dose of these drugs until their complete withdrawal. However, these variables continue to improve after withdrawal so we should consider that the long-term effect of MMF monotherapy is beneficial.

The disparity in the incidence of rejection in the different studies presented should be highlighted, but, nevertheless, they all have in common that rejections occurred in the majority of cases in the first three months after the start of conversion.

The side effects of MMF, such as gastrointestinal complications and hematological problems, were reversed in most cases simply by a temporary reduction in the drug dose so we can consider that the benefits outweigh the risks in this regard.

Therefore, special care should be taken to have an adequate degree of immunosuppression, to analyze well as to when after LTx we should consider the switch to MMF monotherapy and when we should completely withdraw the CNI because we must select very carefully the patients who may benefit from this therapy.

Based on all the studies analyzed, we can infer that the ideal patient for long-term withdrawal of CNI is a patient who clearly has CNI-induced CRF and is not on dialysis, who has not suffered severe acute rejection episodes in the last year, and who has not shown intolerance to MMF previously.

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