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Conversion from Calcineurin Inhibitor-Based Immunosuppression to Mycophenolate Mofetil in Monotherapy Reduces Risk of *De Novo* Malignancies After Liver Transplantation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDE 1 Diego Aguiar
BCDE 1 Diego Martínez-Urbistondo
DE 2,3,4 Delia D'Avola
DE 2,3,4 Mercedes Iñarrairaegui
DE 3,4,5 Fernando Pardo
DE 3,4,5 Fernando Rotellar
DE 2,3,4 Bruno Sangro
DE 2,3,4 Jorge Quiroga
ACDEF 2,3,4 Jose Ignacio Herrero

1 Department of Internal Medicine, Clinica Universidad de Navarra, Pamplona, Navarra, Spain
2 Liver Unit, Clinica Universidad de Navarra, Pamplona, Navarra, Spain
3 Network Center of Biomedical of Liver and Digestive Diseases Hepáticas y (CIBERehd), Pamplona, Navarra, Spain
4 Institute of Health Research of Navarra (IdiSNA), Pamplona, Navarra, Spain
5 Department of Surgery, Clinica Universidad de Navarra, Pamplona, Navarra, Spain

Corresponding Author: Jose Ignacio Herrero, e-mail: iherrero@unav.es
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Background: Immunosuppression increases the risk of malignancy in liver transplant recipients. The potential impact of mycophenolate mofetil monotherapy on this risk has not been studied.

Material/Methods: The incidence and risk factors for *de novo* malignancies of 392 liver transplant recipients with a survival higher than 3 months and a mean follow-up of 8.5 years were studied.

Results: *De novo* malignancies were diagnosed in 126 patients (32.1%) (64 non-melanoma skin cancer and 81 other malignancies). Sixty-nine patients (18.1%) stopped receiving calcineurin inhibitors and were maintained on mycophenolate mofetil monotherapy. The proportion of time on mycophenolate mofetil monotherapy (obtained after dividing the time on monotherapy by the time until diagnosis of neoplasia/last follow-up) was independently associated with a lower risk of *de novo* malignancy (HR: 0.16, 95% CI: 0.05–0.48; P=0.001), non-melanoma skin cancer (HR: 0.17, 95% CI: 0.03–0.79; P=0.024), and other malignancies (HR: 0.23, 95% CI: 0.07–0.77; P=0.017). Older age and male sex were also associated with a higher risk of malignancy, and transplantation for hepatocellular carcinoma increased the risk of non-melanoma skin cancer.

Conclusions: Mycophenolate mofetil monotherapy is associated with a lower risk of cancer in liver transplant recipients compared with maintenance immunosuppression with calcineurin inhibitors.

MeSH Keywords: **Calcineurin • Liver Transplantation • Mycophenolic Acid • Neoplasm Transplantation**

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Background

One of the most important adverse effects of immunosuppression is the increased risk of malignancy. It is a constant complication in all solid organ transplant recipients [1,2]. The risk of cancer in liver transplant recipients is about 2-fold as compared with age- and sex-matched populations [3]. Thus, cancer is one of the leading causes of late death in liver transplant recipients [4–7]. Strategies for reducing the risk of cancer-related death in transplant recipients have been focused on the identification of risk factors for malignancy, such as older age, smoking, alcoholism, and primary sclerosing cholangitis [8–10], the promotion of healthy habits, such as quitting smoking [9], and implementation of screening programs [10–14].

Mycophenolate mofetil (MMF) is frequently used in liver transplant recipients in combination with calcineurin inhibitors (CNI). In the long term, the use of MMF has allowed the reduction or even withdrawal of CNI, achieving an improvement of renal function and of cardiovascular risk factors [15–20], but the effect of MMF monotherapy on the incidence of malignancy has not been studied to date.

The aim of this study is to investigate whether the discontinuation of CNI and maintenance of MMF monotherapy has an influence on the risk of developing neoplasia after liver transplantation. Additional aims of the study were the assessment of the cumulative incidence of post-transplant neoplasia and the risk factors associated with *de novo* malignancy after liver transplantation.

Material and Methods

Study population

The protocol of the study (JHS-MIC-2010-01) was reviewed by the Spanish Agency for Health Products (AEMPS) and was approved by the Clinical Investigation Ethics Committee of Navarra (Spain) with the EO 3/2014 in February 2014. Because it was a retrospective study and some of them had died, patients were not asked to provide consent to participate.

The patient cohort for this study consisted of adult liver transplant recipients receiving their transplant between April 1990 and December 2013 at the Clínica Universidad de Navarra (Pamplona, Spain), with post-transplant survival longer than 3 months (no case of *de novo* malignancy was diagnosed before 3 months). All the patients received CNI (cyclosporine or tacrolimus) starting in the first post-transplant week. Patients who started therapy with sirolimus or everolimus before 3 months were excluded from the study. If sirolimus or everolimus were introduced more than 3 months after transplantation, patients were followed until then and censored at that time. Patients who completely stopped receiving immunosuppression [21] were censored at the time of withdrawal.

Data collection

Data collection was based on written medical records and digital information.

- Pre-transplant medical history. The following data were recorded: age, sex, smoking history, indication of liver transplantation, and MELD score. Indications of liver transplantation were divided in 3 categories (alcoholic liver disease, post-hepatitis C cirrhosis, and others). The presence or absence of hepatocellular carcinoma was also recorded.

- Immunosuppressive therapy. All the patients received CNI-based immunosuppression. From 1990 to 1995, the immunosuppression consisted of the combination of cyclosporine, azathioprine, and corticosteroids. From 1996 to 2004, azathioprine use was gradually reduced and cyclosporine was gradually replaced by tacrolimus. Starting in 1997, MMF was initially used in cases of CNI toxicity [19,22] to allow dose reductions or withdrawal of CNI. In 2004, MMF was added to CNI, and they were combined with steroids between 2004 and 2010. From 2011 to date, most patients received tacrolimus and MMF, without steroids.

- Post-transplant medical evaluation. The program of periodic clinical examination has been previously published [12]. After discharge, patients were followed in the outpatient clinic every week until the end of the first postoperative month, twice a month until the end of the third month, monthly between the third and the sixth month, and every 2 months between the sixth and the twelfth month. Thereafter, patients were seen every 3 months. Post-transplant screening for neoplasia has evolved over time. Since 1990, urinalysis, chest X-ray film, and abdominal ultrasound were done every 6 months during the first year and yearly thereafter. Mammography was repeated every 2 years for all women. Colonoscopy was repeated at 1 year after transplantation for those patients with adenomatous polyps in their baseline colonoscopy and every 2-4 years if new adenomatous polyps were found. When no polyps were detected, colonoscopy was repeated every 7–10 years in patients over 50 years of age. Patients with a smoking history above 20 pack-years who were actively smoking, or had quit smoking less than 10 years before, were seen every year in the ear-nose-throat outpatient clinic (since 2000) and had a yearly low-radiation computed tomography scan (since 2006). Male patients older than 55 years were tested every year with a prostate-specific antigen determination (since 2002). Although this screening protocol was designed for all patients (according

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to their risks), the adherence to the protocol was not complete throughout the study period.

Statistical analysis

All the analyses were performed using IBM SPSS version 20 for Windows software.

Data are expressed as frequency and percentages or mean and standard deviation, as appropriate.

The Kaplan-Meier method was used to obtain actuarial rates of neoplasia. Comparison between groups was performed with the log-rank test (categorical variables) and univariate Cox regression. If P <0.2 in univariate analysis, variables were entered into multivariate Cox analysis to identify factors independently related to neoplasia, not including tumor recurrence in patients transplanted for malignant disease.

The variables that were analyzed as potentially related to the development of neoplasia were: age, sex, smoking (defined as a cumulative smoking of 20 pack-years or more), alcoholic liver disease, post-hepatitis C cirrhosis, hepatocellular carcinoma, primary CNI (cyclosporine or tacrolimus), and MMF monotherapy score. This score was obtained by dividing the time of MMF monotherapy by the time elapsed between transplantation and the diagnosis of neoplasia/last follow-up. This score could theoretically range between 0 (patients on CNI during the whole period of study) and 1 (patients that theoretically had been on MMF monotherapy during the whole period of study).

Results

General characteristics of the patients

Between 1990 and 2013, there were 437 adult patients transplanted in our hospital. Forty-five patients were excluded because their post-transplant survival was below 3 months (N=18), sirolimus or everolimus were started before the third post-transplant month (N=20), or there was inadequate information about their evolution (N=7). Thus, 392 patients were included in the study. They were followed during 3355 patient-years (mean follow-up: 8.5 years) (Figure 1).

The general characteristics of the 392 patients included in the study were the following. There were 308 males (78.6%) and 84 females (21.4%), and their mean age was 56.2±9.2 years. Their mean MELD score was 13.9±5.6. Their indications for transplantation were: alcoholic cirrhosis, 166 patients (42.3%); post-hepatitis C cirrhosis, 120 patients (30.6%); post-hepatitis B cirrhosis, 29 patients (7.4%); primary biliary cirrhosis, 13 patients (3.3%); cryptogenic cirrhosis/non-alcoholic steatohepatitis, 12

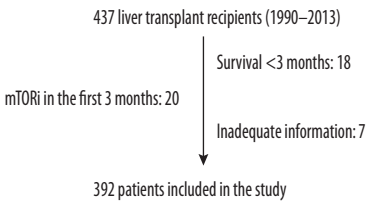

Figure 1. Flow-chart of patients included in the study. In the study period (1990–2013), 437 patients were transplanted, 45 were excluded, and 392 were included in the study. mTORi – mammalian target of rapamycin inhibitors.

patients (3.1%); and other indications, 52 patients (13.2%). There were 129 patients (32.9%) with hepatocellular carcinoma; 178 patients (45.4%) had excessive alcohol consumption; and 131 (33.4%) were smokers before transplantation.

All the patients received CNI-based immunosuppression: cyclosporine-based, 121 patients (30.9%); and tacrolimus-based, 271 (69.1%). Sixty-nine patients (18.1%) withdrew CNI and reached MMF monotherapy after a mean of 70.4±47.8 months after transplantation. The mean duration of MMF monotherapy was 74.9±48.3 months. Table 1 shows the comparison of patients that reached/did not reach MMF monotherapy. Patients reaching MMF monotherapy had significantly higher pre-transplant MELD scores and a lower proportion of them had hepatitis C.

The 1-, 5-, and 10-year actuarial survival rates of the patients included in the study were 93.8%, 83.5%, and 67.2%, respectively.

De novo neoplasia following liver transplant.

After transplantation, 126 patients (32.1%) developed *de novo* malignancies (Figure 2A). The 5- and 10-year actuarial rates were 21.7% and 39.4%, respectively. Sixty-four of them developed 98 non-melanoma skin cancers (NMSC) (Figure 2B). The 5- and 10-year actuarial rates were 11.7% and 21%, respectively.

Eighty-one patients developed other malignancies (Figure 2C). The 5- and 10-year actuarial rates were 12.4% and 25.7%, respectively. The most frequent were genitourinary cancers (23 patients: 10 prostate adenocarcinomas and 13 kidney and urothelial tract cancers), digestive tract cancers (7 esophageal, 3 colorectal, 3 gastric and 3 pancreatic carcinomas, 1 carcinoid tumor, and 3 *de novo* hepatocellular carcinomas), lung cancer (13 patients), non-Hodgkin lymphomas (12 patients), and head and neck cancers (11 patients). Other malignancies were diagnosed in 10 cases. Eight patients had 2 different malignancies (other than NMSC).

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Table 1. Comparison of the patients that reached and did not reach MMF monotherapy.

	MMF monotherapy (N=69)		No MMF monotherapy (N=323)		P
Age (years)	57.0	(9.2)	56.0	(9.2)	NS
Gender					
Male	58	(19%)	250	(81%)	NS
Female	11	(13%)	73	(87%)	
Indication of LT					
Hepatitis C	10	(8%)	110	(92%)	0.001
Alcoholic abuse	37	(21%)	141	(79%)	NS
Other	22	(21%)	84	(79%)	NS
HCC	21	(16%)	108	(84%)	NS
MELD score	15.5	(6.1)	13.6	(5.5)	0.022
Smoking	17	(13%)	114	(87%)	NS
Initial immunosuppression					
Cyclosporine	25	(21%)	96	(79%)	NS
Tacrolimus	44	(16%)	227	(84%)	

HCC – hepatocellular carcinoma; NS – non significant.

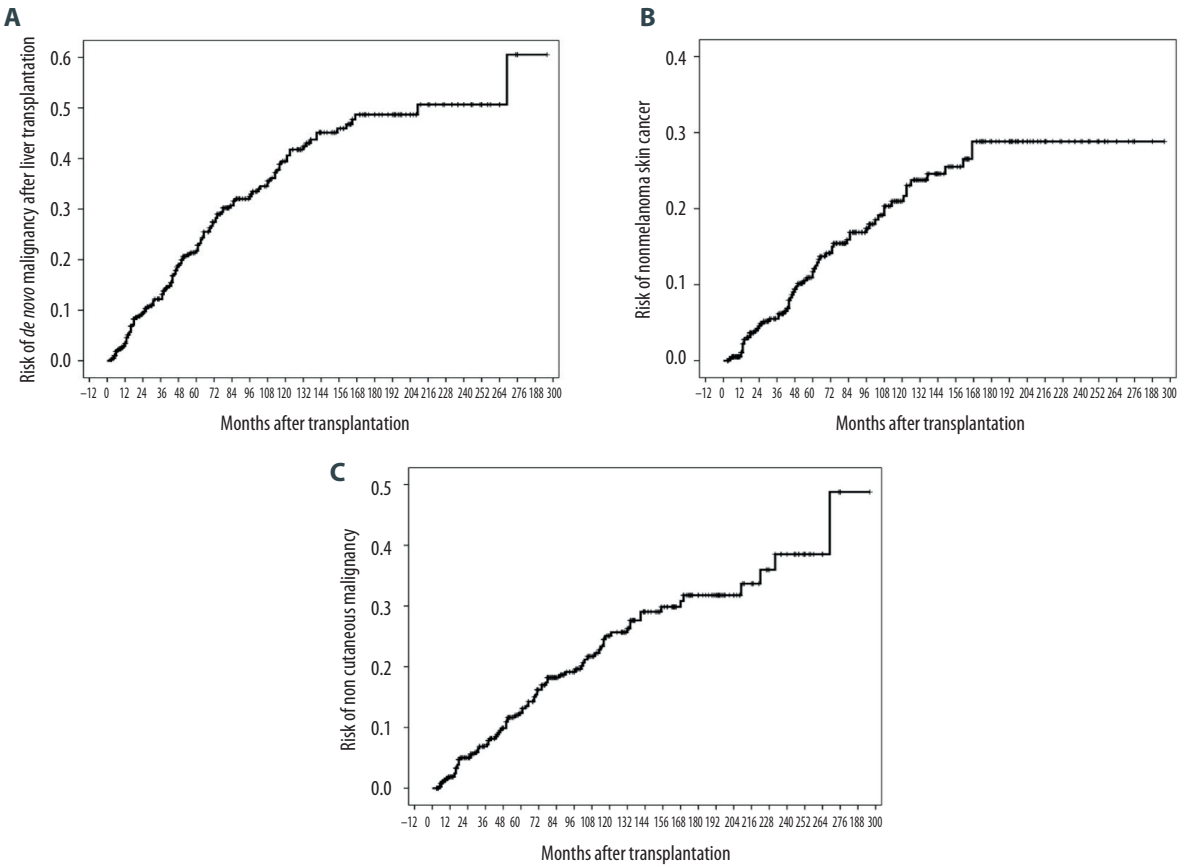

Figure 2. Actuarial risk of *de novo* malignancy after liver transplantation in a series of 392 patients with follow-up longer than 3 months. (**A**) Risk of any malignancy. (**B**) Risk of non-melanoma skin cancer. (**C**) Risk of other malignancies (different from non-melanoma skin cancer).

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Table 2. Risk factors of *de novo* malignancy after liver transplantation in 392 patients. Patients with a higher proportion of time on MMF monotherapy had a lower risk of malignancy.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender (male)	1.98 (1.420–3.26)	0.004	1.89 (1.12–3.20)	0.017
Age (years)	1.06 (1.04–1.09)	<0.001	1.07 (1.04–1.09)	<0.001
HCC*	2.07 (1.44–2.96)	<0.001	1.33 (0.91–1.95)	0.142
Smoking	1.33 (0.90–1.97)	0.155	1.15 (0.77–1.72)	0.487
MMF score**	0.24 (0.08–0.68)	0.002	0.16 (0.05–0.48)	0.001

* HCC – hepatocellular carcinoma; ** MMF score – proportion of time on MMF monotherapy until malignancy or end of follow-up.

Table 3. Risk factors of *de novo* non-melanoma skin cancer after liver transplantation in 392 patients. Patients with a higher proportion of time on MMF monotherapy had a lower risk of skin malignancy.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender (male)	1.87 (0.92–3.79)	0.081	1.93 (0.92–4.04)	0.083
Age (years)	1.08 (1.05–1.12)	<0.001	1.08 (1.04–1.12)	<0.001
HCC*	2.68 (1.63–4.39)	<0.001	1.71 (1.01–2.90)	0.047
Hepatitis C	1.66 (1.00–2.74)	0.048	1.46 (0.87–2.45)	0.153
MMF score**	0.21 (0.05–0.89)	0.034	0.17 (0.03–0.79)	0.024

* HCC – hepatocellular carcinoma; ** MMF score – proportion of time on MMF monotherapy until malignancy or end of follow-up.

Table 4. Risk factors of *de novo* non-cutaneous malignancy after liver transplantation in 392 patients. Patients with a higher proportion of time on MMF monotherapy had a lower risk of non-cutaneous malignancy.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender (male)	2.29 (1.18–4.44)	0.015	1.83 (0.90–3.73)	0.097
Age (years)	1.05 (1.02–1.08)	<0.001	1.05 (1.02–1.09)	<0.001
HCC*	1.91 (1.22–3.00)	0.005	1.34 (0.83–2.16)	0.234
Alcohol	1.41 (0.91–2.18)	0.126	1.33 (0.83–2.14)	0.240
Smoking	1.88 (1.18–2.90)	0.008	1.46 (0.89–2.39)	0.131
MMF score**	0.37 (0.10–1.09)	0.069	0.23 (0.07–0.77)	0.017

* HCC – hepatocellular carcinoma; ** MMF score – proportion of time on MMF monotherapy until malignancy or end of follow-up.

Risk factors of malignancy

Risk factors of *de novo* malignancy are shown in Table 2. In univariate analysis, older age, male sex, history of smoking, hepatocellular carcinoma, and a lower proportion of time on MMF monotherapy (MMF monotherapy score) were associated with higher risk of malignancy. In multivariate analysis, older age (HR per year: 1.07; 95% CI: 1.04–1.09), male sex (HR: 1.89; 95% CI: 1.12–3.20), and MMF monotherapy score (HR: 0.16; 95% CI: 0.05–0.48) were independently associated with the risk of malignancy.

Risk factors of *de novo* NMSC are shown in Table 3. In univariate analysis, older age, hepatitis C, hepatocellular carcinoma,

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and lower MMF monotherapy score were associated with higher risk of cutaneous malignancy. In multivariate analysis, older age (HR per year: 1.08; 95% CI: 1.04–1.12), and MMF monotherapy score (HR: 0.17; 95% CI: 0.03–0.79) were independently associated with the risk of cutaneous malignancy.

Risk factors of *de novo* other malignancies are shown in Table 4. In univariate analysis, older age, male sex, smoking, hepatocellular carcinoma, and lower MMF monotherapy score were associated with higher incidence of non-cutaneous malignancy. In multivariate analysis, older age (HR per year: 1.05; 95% CI: 1.02–1.09) and MMF monotherapy score (HR: 0.23; 95% CI: 0.07–0.77) were the only independent predictors.

Discussion

The most interesting finding of this study is the association between immunosuppression based on MMF monotherapy and a lower risk of malignancy. This finding has been confirmed both for NMSC and for non-skin malignancies. This is an important finding, as malignancies are one of the leading causes of late mortality after liver transplantation [4–7,23].

Numerous studies have shown that liver and other solid organ transplantations increase the risk of malignancy [1,2]. Immunosuppressive drugs are responsible for the increased risk of neoplasia, but it is not clear if this increased risk is the result of the intensity of immunosuppression or that some immunosuppressive drugs may be more oncogenic than others.

Some studies have suggested an association between the intensity of immunosuppression and the risk of malignancy. In a randomized trial, renal transplant recipients receiving a reduced exposure to cyclosporine had a lower risk of malignancy than patients receiving conventional exposure [24]. Similarly, Carenco et al. found a dose-effect relationship between mean blood concentration of tacrolimus and risk of solid cancers after liver transplant [25].

Mammalian target of rapamycin (mTOR) inhibitors have both immunosuppressive and anticarcinogenic effects [26]. The use of mTOR inhibitor-based immunosuppression has been associated with reduced incidence of NMSC following kidney [27] and liver [28] transplantation. Sirolimus has also been used in the prevention of recurrent NMSC [29]. However, the effects of mTOR inhibitors on the risk of other cancers are less well defined [28,30,31].

MMF is another immunosuppressive drug with potential anti-cancer activity. MMF inhibits tumor cell growth and angiogenesis *in vitro*, but this effect has not been translated to clinical anti-cancer efficacy [32]. In a single-center study, the combination of MMF and CNI in renal transplant recipients was associated with a higher risk of malignancy than were other immunosuppressive regimens [33]. In contrast with these results, multicenter studies have shown that renal, cardiac, and liver transplant recipients who receive MMF have a lower (or, at least, not higher) risk of malignancy than patients without MMF [34–36].

The results presented here are in agreement with these multicenter studies. However, these studies investigated regimens containing MMF and CNI. In our study, we investigated the effect of MMF when it is used in monotherapy in the long term. Use of MMF monotherapy has been associated with rejection in some cases [37], but MMF monotherapy is safely achieved in most cases when CNI are gradually reduced [19,20]. It is unclear if the reduction in the incidence of malignancy is the consequence of a reduction in the net immunosuppression, the interruption of the carcinogenic effect of CNI, or the potential anti-cancer activity of MMF.

Other results of this study are less surprising. The association between older age and higher risk of malignancy or the association between HCC and NMSC have been previously described in liver and other solid organ transplant recipients [8,38].

This study has several limitations. It is a single-center study, with a retrospective design. The immunosuppression of the patients included in the study was modified according to complications of standard CNI-based therapy. Thus, the groups had different sizes and a potential unrecognized bias could have affected the results. Multicenter and (ideally) prospective studies are needed to confirm these results. We believe this is the first study showing that MMF monotherapy may be associated with a lower risk of malignancy after liver transplantation.

Conclusions

The cumulative incidence of *de novo* malignancy in this single-center study, including 392 patients with more than 3 months of post-transplant survival, was higher than 30% after a mean follow-up of 8.5 years. Male sex and older age were related to a higher risk of cancer, and HCC was related to a higher risk of NMSC. Our results suggest that the risk of post-transplant cancer decreases when CNIs are interrupted and immunosuppression is maintained with MMF monotherapy. We found an inverse dose-response relationship (a lower rate of malignancy as the proportion of time on MMF monotherapy increases) that is independent of other factors predictive of malignancy. MMF monotherapy in liver transplant recipients could significantly reduce the risk of *de novo* malignancy.

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