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Abbreviations: CKD, chronic kidney disease; CNI, calcineurine inhibitors; TDM, therapeutic drug monitoring; GFR, glomerular filtration rate; LT, liver transplantation; MMF, mycophenolate mofetil; MPA, mycophenolate acid.

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Declaration of interest

Sebastien Dharancy reports receiving lecture fees from Novartis, Abbvie, Gilead, Astellas, and Bayer and serving as a board member of Novartis and Nanobiotix. None of these activities presents a conflict of interest concerning this work. Jérôme Dumortier has been a clinical investigator, speaker and/or consultant for Astellas, Gilead Sciences, Janssen Pharmaceuticals, Novartis and Roche. None of these activities presents a conflict of interest concerning this work.

Autorship

GL, JD and SD: conception and design of the study, acquisition of data, analysis and interpretation of data. FSM and PM: analysis and interpretation of data. ME, JB, EB, GM, MN, ST, VC, OG, OB, AL, PM, GL, FRP: acquisition of data. All the authors: final approval of the version.

Abstract

Background: Mycophenolate mofetil (MMF) monotherapy following liver transplantation (LT) remains controversial due to a risk of acute rejection. The aim of this study was to report the largest multicenter experience of the use a MMF monotherapy guided by therapeutic drug monitoring using pharmacoslope modeling and Bayesian estimations of the MPA inter-dose AUC ($_{BE}AUC^{MPA}$) before withdrawing calcineurin inhibitors (CNI) and to evaluate the benefit of MMF monotherapy. **Methods**: MMF daily doses were adjusted to reach the $_{BE}AUC^{MPA}$ target of 45 µg.h/mL. Then CNI were withdrawn and patients were followed on liver test and clinical outcomes. **Main findings:** From 2000-2014, in 2 transplantation centers, 94 liver transplant recipients received MMF monotherapy 6.5±4 years after LT. The mean $_{BE}AUC^{MPA}$ was 45.5±16 µg.h/mL. During follow-up, 4 patients experienced acute rejection (4%). During the first year, estimated glomerular filtration rate (eGFR) improved from 46.2±10.5 to 49.1±11.5 mL/kg/min (p=0.025). Benefit persisted at year 5. In patients with metabolic syndrome, eGFR did not improve. **Conclusion**: MMF monotherapy regimen appears usually safe and beneficial, with low risk of acute rejection and eGFR improvement. Therapeutic drug monitoring strategy seemed useful by identifying 14% of patients with low MMF exposure.

Keywords: Liver transplantation, Acute rejection; Mycophenolate mofetil, Chronic kidney dysfunction.

Introduction

Calcineurin inhibitors (CNI) are still the basis of immunosuppressive regimens after liver transplantation (LT), and their combination with other immunosuppressants has improved graft and recipient survival since the 1980s. However, early and chronic exposure to CNI induces side effects such as chronic kidney disease (CKD). On average, moderate but significant CKD (Stage 2–3) occurs in 40–50% of LT recipients and severe CKD (Stage 4) in 5–15%, 5 years post-LT, reducing long term survival (1, 2). Thus, different prophylactic and corrective strategies using new immunosuppressive combinations and regimens have been developed to avoid the onset of CKD (3): excluding CNI from immunosuppressive regimens; delaying their introduction; early withdrawal/minimization and conversion to mTOR inhibitors (4-5). The latter is a promising recent approach but it faces to a substantial rate of adverse events. One of the first historical approach was to minimize CNI under the cover of mycophenolate mofetil (MMF) use. This latter strategy was generally associated with an improvement in serum creatinine in 60–80% of patients and an increase of GFR by 9–12 ml/min (3). Although the so-called "CNI sparing strategy" reduces CNI exposure and improves renal function (6) it was not as successful as CNI withdrawal followed by MMF monotherapy.

A meta-analysis of controlled and non-controlled trials of CNI withdrawal followed by MMF monotherapy showed a 4.5-fold increased risk of acute rejection (7). Conversely, we have previously shown, as others, in a previous pilot study that MMF monotherapy may be administered to a selected group of maintenance liver transplant patients with a very low risk of acute rejection (8-9). Therapeutic drug monitoring (TDM) of mycophenolate acid (MPA), the active compound of MMF, may be a useful tool to limit the risk of rejection as well as the risk of drug toxicity. Several consensus conferences have recommended targeting an MPA area under the curve ($AUC_{0\text{-}12h}$) of 30 to 60 µg.h/mL in patients with low to intermediate

immunological risk (10). The pharmacological benefit of TDM of MPA has been demonstrated in a retrospective multicenter study in about 7000 kidney transplant patients showing that MMF dose adjustment based on the MPA AUC by pharmacoslope modeling and a Bayesian estimation ($_{BE}AUC^{MPA}$), significantly reduced intra-individual and inter-individual variability of MMF exposure, and minimized the frequency of both under- and overexposure (11). Bayesian estimators make it possible to calculate the AUC and dose adjustments to reach the optimal target window with a limited number of blood samples and a pharmacoslope model (12).

Taking into account all of these data, the main goals of this real life study were to report our clinical practice experience with MMF monotherapy under the cover of dose-adjusted MMF guided by $_{BE}AUC^{MPA}$ in a large cohort of adult liver transplant recipients with severe CNI-induced side effects and show its efficacy and safety.

PATIENTS AND METHODS

Patients and study design

This is a retrospective, uncontrolled, observational study performed in the liver transplant centers of Lille and Lyon University hospitals in collaboration with the pharmacology and toxicology department of Limoges University hospital. All patients were informed. Ethical committee approved the study [CNIL (Commission Nationale de l'Informatique et Liberté) DEC2015-116]. Patients who belonged to our active cohort of around 1400 transplanted patients were included from October 2000 to December 20014. In our daily clinical practice, MMF monotherapy was proposed to stable, maintenance recipients at least 3 years after LT. The main inclusion criterion of this real life cohort was: adult liver transplant recipient with severe CNI-induced side effects or potential future side effects such

as cancer recurrence. The exclusion criteria were: 1) multi-organ transplant, 2) medical history of severe acute rejection, 3) LT for auto-immune liver diseases, 4) re-transplantation.

Management of immunosuppression

The study design and the therapeutic management for immunosuppression are presented in figure 1. Briefly**,** the initial immunosuppressive regimen included triple therapy with CNI (cyclosporine or tacrolimus), MMF and corticosteroids. Corticosteroids were maintained for 3 to 6 months after LT. Cyclosporine or tacrolimus doses were reduced by steps of 20-25% as soon as severe CNI-induced side effects occurred to target C0 trough levels of 5 ng/mL for tacrolimus and 80 ng/mL for cyclosporine and withdrawal within 6 months. Liver function tests were monitored at each visit during weaning. Before CNI withdrawal, the Bayesien estimation of AUC MPA ($_{BE}AUC^{MPA}$) was estimated using a limited number of blood samples (13).

Determination of MPA concentration

Blood samples were collected in EDTA tubes, plasma was separated by centrifugation. The measurement of total MPA was performed using a validated high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection. Blood serum (500 µL), an internal standard (50 µL) (thiopental in methanol 1 g/L diluted with deproteinized water to 25 mg/L), and calibrators were acidified with hydrochloric acid and extracted with dichloromethane (5 mL). Calibrators were prepared in drug-free plasma and their concentrations were 0, 0.5, 1, 5, 10, and 20 µg/L for MPA. The organic fraction was then evaporated to dryness under a stream of nitrogen. The dry residue was reconstituted with 100-µL elution solvent (KH_2PO_4 buffer/acetonitrile [70/30 v/v] at pH=2.6). Then, the sample (40 µL) was injected into the HPLC system with a steel column Nucleosil C18, 5 µm (250×4.6 mm, id) and with UV detection at 300 nm. The limits of LOD and LOQ were 50 and

200 µg/L, respectively, and calibration curves obtained using quadratic regression from the LOQ to 20,000 µg/L yielded $r^2 > 0.999$.

Bayesien estimation of MPA AUC ($_{BE}AUC^{MPA}$)

The NONMEM version VI (GloboMax LLC) nonlinear mixed-effects population pharmacokinetic model and the Bayesian estimator of a 4-point limited sampling strategy developed at Limoges University Hospital were used to determine MPA area under the blood concentration–time curve ($_{BE}AUC^{MPA}$) (12). Algorithms estimated $_{BE}AUC^{MPA}$ using limited samples: 20 minutes [C_1], 1 hour [C_2] and 3 hours [C_3] after MMF intake. The $_{BE}AUC^{MPA}$ was used to predict the required individual daily dose of MMF before MMF monotherapy. Three daily dose of MMF, adapted for each patient, were obtained for 3 different $_{BE}AUC^{MPA}$ threshold: 30, 45 and 60 µg.h/mL respectively. The 45 µg.h/mL $_{BE}AUC^{MPA}$ threshold of was targeted to avoid acute rejection and the drug sides effects. After potential dose adjustments and once the targeted $_{BE}AUC^{MPA}$ was obtained, CNI was withdrawn and MMF was continued as monotherapy. The $_{BE}AUC^{MPA}$ was only performed once, before CNI withdrawal and was not checked further. Liver function tests were monitored one month after CNI withdrawal and at the physician's discretion thereafter.

Outcomes and endpoints

The primary endpoint was the efficacy of MMF monotherapy, as defined by the absence of acute rejection in a real life experience cohort. The diagnosis of acute liver graft rejection was achieved as usual, after exclusion of differential diagnoses. A liver biopsy was performed when clinically indicated by the onset of disturbances in liver function tests after CNI withdrawal. Acute rejection was classified according to the BANFF scale diagnosis (14). Secondary endpoints were: clinical and biological tolerance to treatment, and slopes over time of the estimated glomerular filtration rate (eGFR) following withdrawal of CNI. The eGFR

was calculated using the MDRD4 formula at each follow-up session and compared to baseline eGFR. Moderate chronic renal failure was defined according to the international consensus as eGFR 30-59 mL/min/1.73m^2 and severe chronic renal failure by eGFR 15-29 mL//min/1.73m^2 (15). The slope of eGFR was also studied in relation to the presence of a metabolic syndrome.

Data and statistical analysis

Data were prospectively collected at baseline: age (years), gender (male), body mass index (BMI, kg/m^2), blood pressure (mmHg), the presence of diabetes and dyslipidemia, metabolic syndrome, cause of cirrhosis, hepatocellular carcinoma at LT, survival data. The following biological data were systematically and prospectively collected when CNI was withdrawn, at 1 month and every year for 5 years: hemoglobin (g/dL), platelets (G/mm^3), leukocytes (10^3/mm^3), Prothrombin time (%), AST (IU/L), ALT (IU/L), γGT (IU/L), ALP (IU/L), bilirubin (mg/L), lipid profile, fasting glucose (mg/dL), glycated hemoglobin (%), creatinine (mg/L). Continuous variables were expressed as means ± standard deviation (SD). Statistical analysis was performed with the software NCSS 9 (Kaysville, USA, 2013). The Chi-square and Mann-Whitney tests were used to compare qualitative and quantitative variables, respectively. The slopes of biological variables over time, as well as of the eGFR, were analysed with the paired T test. The Wilcoxon signed rank paired test was used for non-parametric variables. Three-year patient survival on MMF monotherapy was estimated using the Kaplan Meier test. $P < 0.05$ was considered to be significant.

RESULTS

Cohort characteristics

Ninety-four liver transplant patients (70 men and 24 women, mean age 60.7±8 years old) treated with MMF monotherapy between October 2000 and December 2014 were included. The mean time before MMF monotherapy was begun was 6.5±4 years after LT. The

main reason for CNI withdrawal was CKD (88%). The other reasons were: risk of cancer recurrence (n=7), neurological (n=3) and cardiovascular complications (n=1). Only one patient had morbid obesity but 36% had a metabolic syndrome. All patient characteristics are presented in Table 1.

The main biological characteristics of the cohort are presented in Table 2. The median $_{BE}AUC^{MPA}$ before CNI withdrawal was 45.5±16 (median of 45.4) µg.h/mL. Fourteen percent of patients had a $_{BE}AUC^{MPA}$ below 30 µg.h/mL and required a 30% average increase of the daily dose of MMF to reach the 45µg.h/mL target (the majority of them was treated with 1.5g twice a day after adjustment versus 1g twice before). Among the cohort, 18% of patients had a modification of their daily dose of MMF after the $_{BE}AUC^{MPA}$ dosage and before CNI withdrawal (figure 2).

Follow-up and survival

The mean follow-up was 2.8±2.3 years. The 1-, 3- and 5-year survival rates of patients treated with MMF monotherapy were 94%, 76% and 73% respectively (figure 3). Nineteen patients had died at the final follow-up in the entire cohort. The causes of death were sepsis (n=5), de novo cancer or recurrent hepatocellular carcinoma (n=5), cardiovascular events (n=3), graft failure related to recurrent alcoholic cirrhosis (n=2), and unknown causes (n=4). Although none of the patients required additional LT or a kidney transplant during follow-up, one patient died while waiting for combined liver-kidney transplantation due to chronic renal failure and recurrent cirrhosis.

Efficacy of MMF monotherapy

There was no significant difference in the entire cohort in AST, ALT, γGT or bilirubin from baseline to five years after MMF monotherapy (figure 4). However, an episode of acute rejection occurred in 4 of the 94 patients (4.2%). All the 4 patients had a $_{BE}AUC^{MPA}$ below the 45 µg.h/mL target before the adjustment of MMF dosage (7, 33, 37 and 43 µg.h/mL). Among

these 4 patients, 2 acute rejection were biopsy proven (Banff score of 5 and >7). These two patients received corticosteroid bolus infusions (1g/day for three consecutive days). Three patients had a favourable outcome after the introduction of CNI (n=2) or everolimus (n=1). One of the patients died of liver failure due to acute rejection episode that occurred 6.2 years after CNI was withdrawn. In this specific case, the acute rejection was suspected to be secondary to a MMF withdrawal in a context of insufficient adherence and observance to immunosuppressive regimen.

Tolerance of MMF monotherapy

The leukocyte count did not significantly decrease during MMF monotherapy (supplementary file: figure 1). However 2/94 patients (2%) in the cohort returned to a CNI regimen because of pancytopenia requiring MMF withdrawal. Two patients developed chronic diarrhea attributed to MMF. The outcome was favourable in one of the patients with symptomatic treatment. The second patient had to be switched to enteric-coated mycophenolate sodium salt.

Slopes of eGFR

In the cohort

One year after CNI withdrawal, there was a significant average increase in the eGFR calculated by the MDRD of 6.3% (from 46.2±10.5 to 49.1±11.5 mL/kg/min, p=0.025). This benefit persisted after 5 years (eGFR at 5 years, 53.1±13.5; p=ns). The slopes of eGFR from baseline to 5 years is presented in figure 5.

In patients with moderate to severe CKD

Sensitivity analysis of the subgroup of patients with moderate or severe CKD (eGFR<60ml/kg/min, n=74/94 patients) showed that the average eGFR at one year was significantly increased by 5.1% (from 39.1±10.7 mL/kg/min to 41.2±13 mL/kg/min, p=0.04). This improvement persisted at 5 years (42.8±19 mL/kg/min, p=ns). Sensitivity analysis in

patients with stage 4 CKD (n=17), defined as an eGFR below 30 mL/kg/min showed a significant and even greater increase in eGFR, of +13.5% (from 24.5±4 to 27.8±7.9 mL/kg/min, p=0.05). None of the patients included in the cohort underwent kidney transplantation. Only one patient was on the waiting list for combined renal and liver transplantation, due to the recurrent HCV after LT.

Patients with metabolic syndrome

Metabolic syndrome was identified in 36.1% (34/94) of patients. There was no significant difference at baseline for age, eGFR, liver function tests, or $_{BE}AUC^{MPA}$ in patients with a metabolic syndrome (Table 3). As expected, there were significantly more patients with CKD stage 3 and 4 in the patients with than in those without a metabolic syndrome (87 vs. 69.4%, p=0.03). Also as expected, patients with a metabolic syndrome had a significantly higher BMI and more frequently presented with hypertension, dyslipidemia and diabetes. An analysis of the slopes of eGFR according to metabolic status showed that the eGFR in patients with a metabolic syndrome did not significantly improve during the first year of MMF monotherapy (from 42±13 mL/kg/min to 42.5±16 mL/kg/min, p=0.7) while the average eGFR in those without a metabolic syndrome significantly improved by 7.8% (from 47.3±25 mL/kg/min to 51±27 mL/kg/min, p=0.025).

DISCUSSION

This real life study supports the feasibility of CNI withdrawal for MMF monotherapy regimen without high risk of acute rejection. Furthermore, it suggest the utility of a therapeutic drug monitoring before CNI withdrawal with the identification of 14% of patients, that had a $_{BE}AUC^{MPA}$ lower than 30 µg.h/mL and this threshold has been shown to be associated with a potential risk of acute rejection (10). The beneficial effect of this strategy resulted in a significantly improvement of the eGFR one and 5 years after CNI withdrawal

without a high risk of acute rejection (4%). Even in patients with a stage 4 CKD, none underwent haemodialysis or kidney transplantation.

In our cohort, the rate of acute graft rejection was lower than in previously published studies (6-7). This may be due to: 1) the use of MMF dose adjustment based on the $_{BE}AUC^{MPA}$ before CNI withdrawal; 2) our population of patients who were mainly transplanted for alcoholic cirrhosis (73% of cases), which is known to be associated with a lower rate of acute rejection than other indications of LT (16, 17) ; 3) the 5 years of follow-up after LT without any immunological events before CNI withdrawal. Thus, our patients were at very low risk of rejection. However, an additional control of $_{BE}AUC^{MPA}$ after adjustment seems useful and cautious in order to check that the second result reach effectively the expected target.

Future studies should focus on the Treg profile and tolerance immunity in these patients to understand who could benefit most from this immunosuppressive strategy with minimal risk. Furthermore, we cannot exclude that our patients could have been tolerant and discontinue their maintenance immunosuppression (18). However this strategy for minimizing immunosuppression with CNI withdrawal for MMF monotherapy regimen was usually safe and easy to manage. This option could also allow earlier withdrawal of CNI after LT to reduce morbidity.

Tolerance to this regimen was good, and there were few severe side effects. Hematological tolerance was quite good (only 2 pancytopenia), probably because MMF was not introduced but only dose adjusted. The switch from MMF to mycophenolate sodium salt showed good results for digestive tolerance in one case.

Our results showed a clear improvement in renal function with MMF monotherapy. Seventy-two percent of our cohort had moderate or severe chronic renal failure (eGFR < 60). After a median of follow-up of 3.3±2.6 years none of our patients required renal

transplantation or dialysis. The renal benefit occurred during the first year after CNI withdrawal and persisted for 5 years. However, this improvement did not occur in patients with metabolic syndrome. In these patients, CKD was probably multifactorial and not only due to CNI. Thus the reversibility of CNI nephrotoxicity after withdrawal was insignificant in these patients. Similar data have previously been published, especially on diabetes which has been shown to be an independent predictive factor of the occurrence of CKD.

Other studies have evaluated MMF monotherapy after LT (3). Our study confirms these preliminary results and shows a benefit in renal function after CNI withdrawal in a large cohort of patients. This benefit seems to be more significant in CKD related to CNI without other associated causes (metabolic syndrome). However, this study has limitations because it is retro-prospective. There was no systematic histological evaluation of the liver graft, making the absence of histological impairment impossible to confirm. Nevertheless, there was no significant modification in liver tests. This real life study needs to be confirmed with a randomized controlled approach to prove the benefit of this regimen compared to a sparing strategy combining CNI and MMF.

In conclusion, MMF monotherapy guided by therapeutic drug monitoring of mycophenolate acid is usually safe and effective strategy in LT in patients with severe side effects induced by CNI. This strategy improves renal function during the first year and this persists for up to 5 years. The risk of rejection is quite low if the strategy is proposed to patients transplanted for alcoholic cirrhosis a median 5 years after transplantation and with a ${}_{BE}AUC^{MPA} > 45$ µg.h/mL. The benefit of this strategy should be confirmed in a prospective randomized trial.

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Figure Legends

Figure 1: Study Design

Figure 2: Distribution of MPA dosage before dosage adjustment.

Figure 3: Three years survival of the whole cohort using Kaplan Meier analysis. Time 0 corresponds to the beginning of MMF monotherapy.

Figure 4: Slopes of liver function tests from baseline to 5 years using paired t-test. a) AST; b) ALT; c) γGT and d) total bilirubin. Each dot corresponds to a patient and horizontal bar represents the mean at each point of analysis.

Figure 5: Slopes of eGFR in the whole cohort (n=94). The dots represent mean±SD.

Tables

Table 1: Clinical characteristics of the whole cohort (n=94) at baseline (Baseline corresponds to the first day of MMF monotherapy).

Patients Characteristics (n=94)	
Male gender, n (%)	70 (74.5%)
Age (years), mean±SD	60.7±8
Time (years) between LT and MMF monotherapy, mean±SD	6.5±5
Reasons for CNI withdrawal, n (%)	CKD, n=83 (88%) Other, n=11 (12%)
Causes of cirrhosis, n (%)	Alcohol, n=69 (73%) HCV/ HBV, n=14 (15%) Other, n=11 (12%)
HCC*, n (%)	42 (45%)
Diabetes, n (%)	41 (44%)
Dyslipidemia, n (%)	44 (47%)

BMI >30 kg/m^2	27 (34%)
Arterial hypertension, n (%)	81 (86%)
Metabolic syndrome	34 (36%)

*HCC, hepatocellular carcinoma

Table 2: Biological characteristics of the whole cohort at baseline

Biological Characteristics (n=94)	**Baseline Value**
AST (IU/L)	24±17
ALT (IU/L)	21±13
Total Bilirubin (mg/L)	5.8±3.3
γGT (IU/L)	65±108
Alkaline phosphastase (IU/L)	154±184
eGFR (MDRD) (mL/kg/min)	46.2±10.5
Haemoglobin (g/dL)	12.4±1.9
Platelets (10^3/mm3)	214.7±71
Leukocytes (10^3/mm^3)	5.9±1.8
Glycated HbA1c (%)	6±1.3
Total Cholesterol (g/L)	1.95±0.6
Serum triglycerides (g/L)	1.8±1.3
Protrombin Time (%)	96±6

Table 3: Comparison of characteristics at baseline between patients with and without a metabolic syndrome.

Characteristics	**No Metabolic syndrome (n=60)**	**Metabolic syndrome (n=34)**	**p value**
Age (years)	60.2±9	61.1±7	
BMI (kg/m²)	24.3±4.8	31.2±4.6	<0.0001
Diabetes (%)	34	65.5	<0.0001
Arterial Hypertension (%)	72	100	<0.0001
Dyslipidemia (%)	26	85	<0.0001
HbA1c (%)	5.7±0.9	7.1±1.7	0.01
Total Cholesterol (g/L)	1.8±0.5	2.16±0.6	0.02
Serum Triglycerides (g/L)	1.6±0.9	2.4±1.7	0.009
eGFR <60 (%)	69	87	0.03
eGFR	49.7±25	44.4±14	ns
AST (IU/L)	25±12	20±8	ns
ALT (IU/L)	21±10	19±11	ns
Total Bilirubin (mg/L)	6.6±3.6	4.9±3	ns
PAL (IU/L)	136±37	172±90	ns
γGT (IU/L)	48.7±29	82±43	ns
$_{BE}AUC^{MPA}$	43.8±18	46.3±11	ns

Figure 1

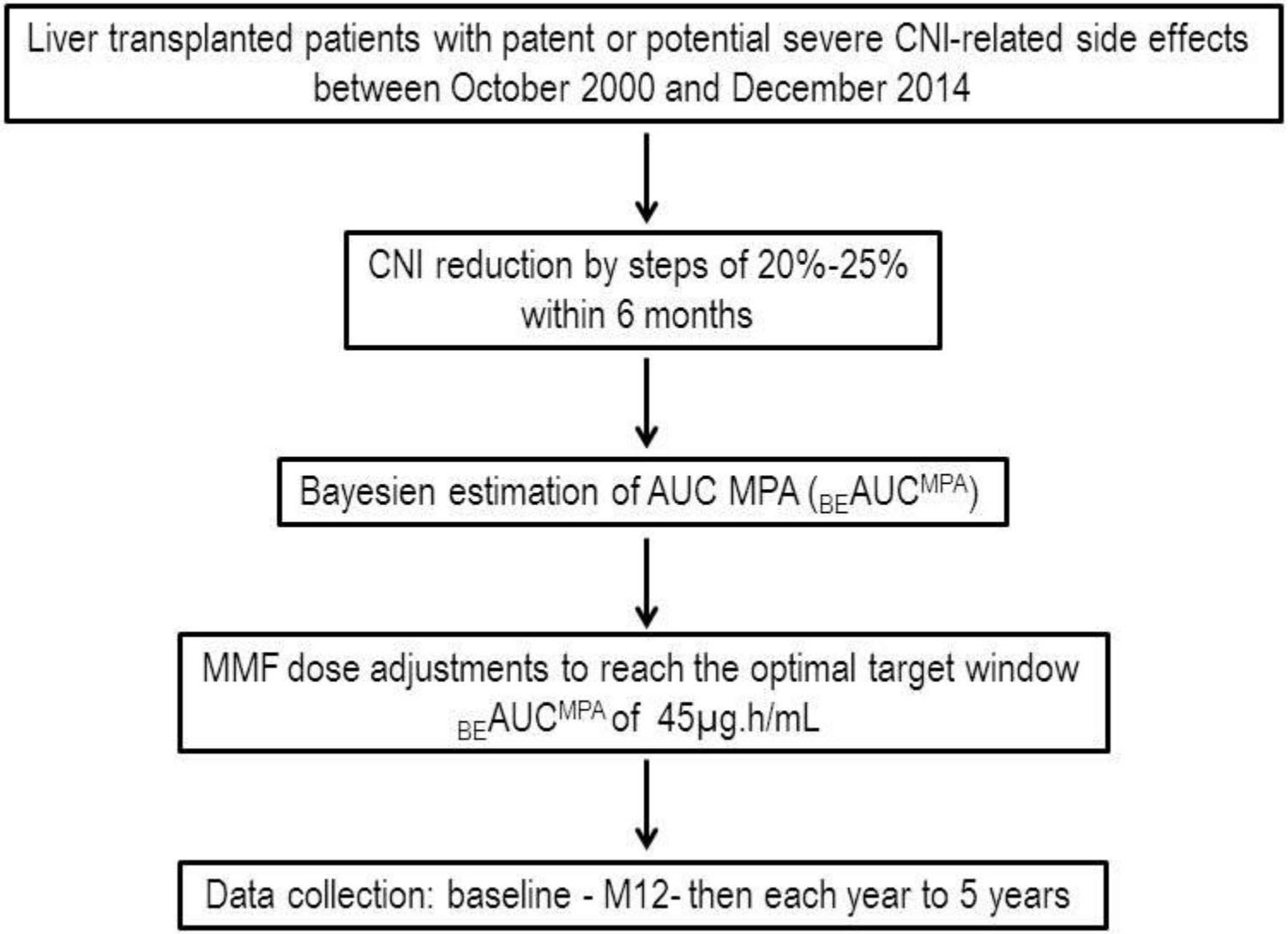

Liver transplanted patients with patent or potential severe CNI-related side effects between October 2000 and December 2014
CNI reduction by steps of 20%-25% within 6 months
Bayesien estimation of AUC MPA ($_{BE}AUC^{MPA}$)
MMF dose adjustments to reach the optimal target window $_{BE}AUC^{MPA}$ of 45µg.h/mL
Data collection: baseline - M12- then each year to 5 years

Figure 2

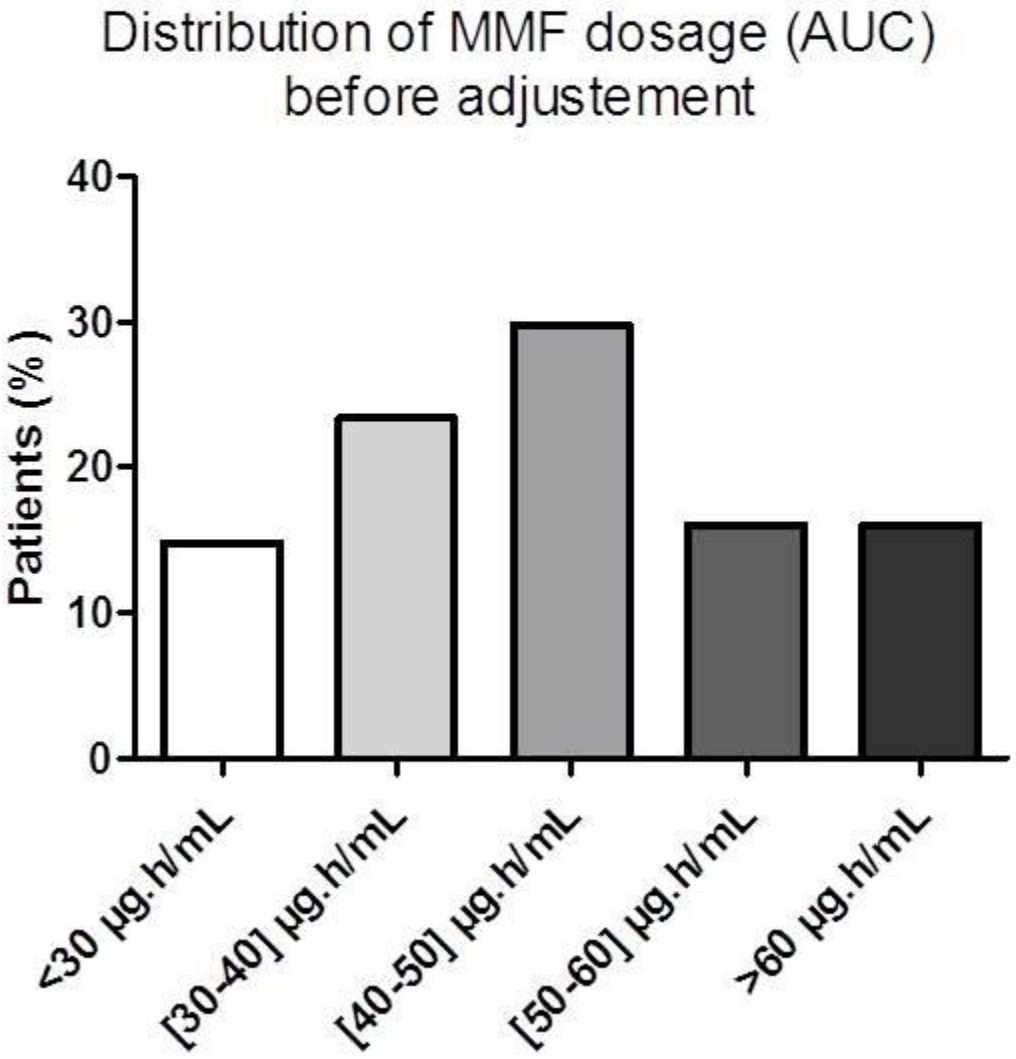

Distribution of MMF dosage (AUC)
before adjustement
Patients (%)
40
30
20
10
0
<30 µg.h/mL
[30-40] µg.h/mL
[40-50] µg.h/mL
[50-60] µg.h/mL
>60 µg.h/mL

Figure 3

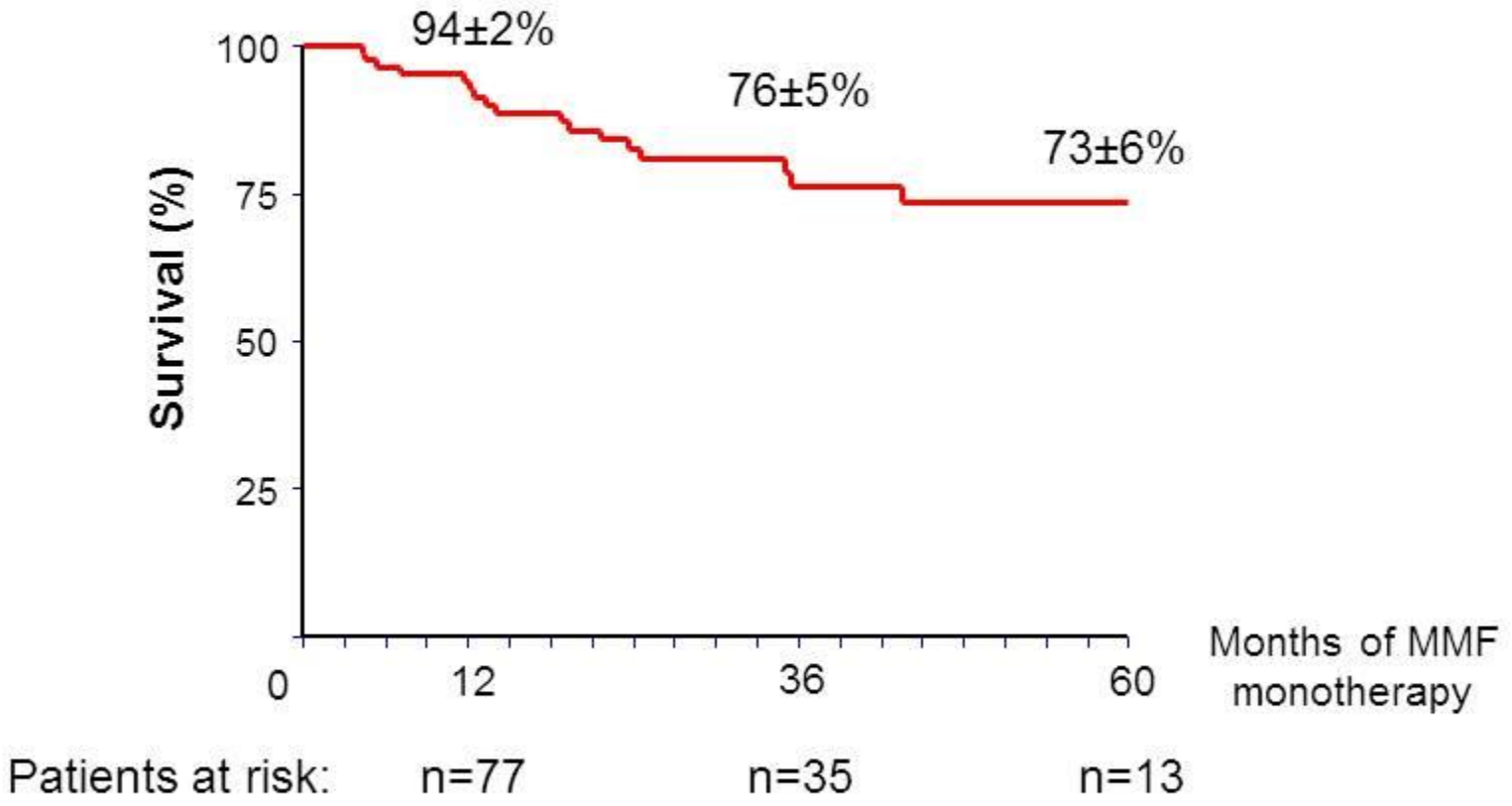

94±2%
76±5%
73±6%
100
75
50
25
Survival (%)
0
12
36
60
Months of MMF monotherapy
Patients at risk:
n=77
n=35
n=13

Figure 4

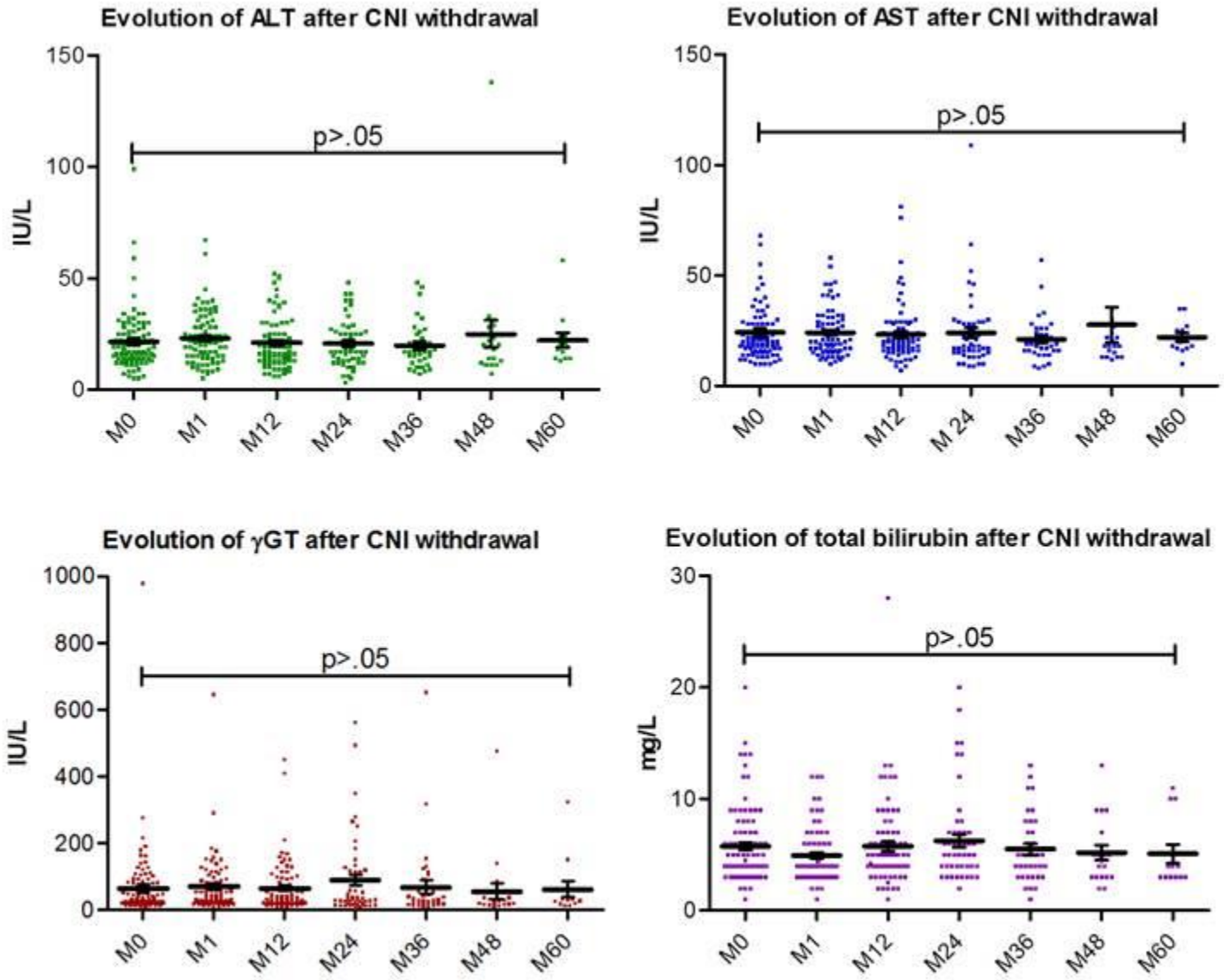
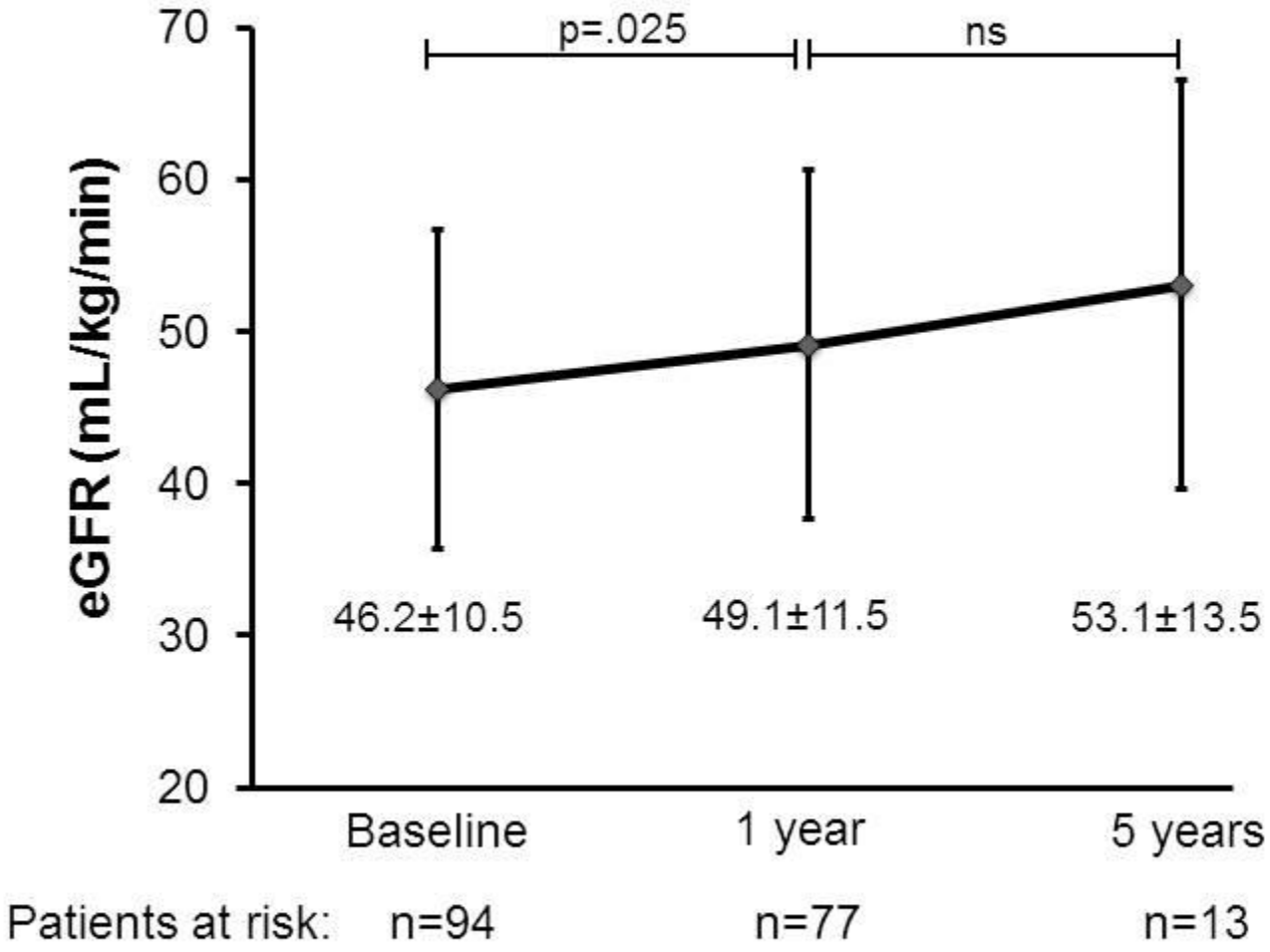

Evolution of ALT after CNI withdrawal
IU/L
150
100
50
0
p>.05
M0
M1
M12
M24
M36
M48
M60
Evolution of AST after CNI withdrawal
IU/L
150
100
50
0
p>.05
M0
M1
M12
M 24
M36
M48
M60
Evolution of γGT after CNI withdrawal
IU/L
1000
800
600
400
200
0
p>.05
M0
M1
M12
M24
M36
M48
M60
Evolution of total bilirubin after CNI withdrawal
mg/L
30
20
10
0
p>.05
M0
M1
M12
M24
M36
M48
M60

Figure 5


p=.025
ns
70
60
50
40
30
20
eGFR (mL/kg/min)
46.2±10.5
49.1±11.5
53.1±13.5
Baseline
1 year
5 years
Patients at risk: n=94 n=77 n=13