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Real-World Multicenter Experience of Immunosuppression Minimization Among 661 Liver Transplant Recipients

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

BC 1 Diego Aguiar
BC 1 Diego Martínez-Urbistondo
B 2,3 Alberto Baroja-Mazo
B 2,4,5 Manuel de la Mata
B 2,4,5 Manuel Rodríguez-Perálvarez
B 2,6 Angel Rubín
B 6 Lorena Puchades
B 7 Trinidad Serrano
B 7 Jessica Montero
B 8 Antonio Cuadrado
B 8 Fernando Casafont
B 2,9 Magdalena Salcedo
B 9 Diego Rincón
ABDFG 2,3,10 Jose A. Pons*
ABCDEFG 1,2,11 Jose I. Herrero*

1 Liver Unit, University Clinic of Navarra, Pamplona, Spain
2 Network for Biomedical Research for Hepatic and Digestive Diseases (CIBERehd), Pamplona, Spain
3 Murcia Institute for Biomedical Research (IMIB-Arrixaca), Pamplona, Spain
4 Liver Unit, Reina Sofia University Hospital, Córdoba, Spain
5 Maimónides Institute of Biomedical Research (IMBIC), Córdoba, Spain
6 Liver Unit, La Fe University Hospital, Valencia, Spain
7 Gastroenterology Service, Lozano Blesa University Hospital, Zaragoza, Spain
8 Gastroenterology Service, Marques de Vadecilla University Hospital, Santander, Spain
9 Gastroenterology Service, Gregorio Marañon University Hospital, Madrid, Spain
10 Gastroenterology and Hepatology Division and Liver Transplantation Unit, Virgen de la Arrixaca University Hospital, Murcia, Spain
11 Institute for Health Investigation of Navarra (IdiSNA), Pamplona, Spain

* Both authors share senior authorship

Corresponding Author: Jose I. Herrero, e-mail: iherrero@unav.es

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Background: Long-term morbidity and mortality in liver transplant recipients is frequently secondary to immunosuppression toxicity. However, data are scarce regarding immunosuppression minimization in clinical practice.

Material/Methods: In this cross-sectional, multicenter study, we reviewed the indications of immunosuppression minimization (defined as tacrolimus levels below 5 ng/mL or cyclosporine levels below 50 ng/mL) among 661 liver transplant recipients, as well as associated factors and the effect on renal function.

Results: Fifty-three percent of the patients received minimized immunosuppression. The median time from transplantation to minimization was 32 months. The most frequent indications were renal insufficiency (49%), cardiovascular risk (19%), *de novo* malignancy (8%), and cardiovascular disease (7%). The factors associated with minimization were older age at transplantation, longer post-transplant follow-up, pre-transplant diabetes mellitus and renal dysfunction, and the hospital where the patients were being followed. The patients who were minimized because of renal insufficiency had a significant improvement in renal function (decrease of the median serum creatinine level, from 1.50 to 1.34 mg/dL; P=0.004). Renal function significantly improved in patients minimized for other indications, too. In the long term, glomerular filtration rate significantly decreased in non-minimized patients and remained stable in minimized patients.

Conclusions: Immunosuppression minimization is frequently undertaken in long-term liver transplant recipients, mainly for renal insufficiency. Substantial variability exists regarding the use of IS minimization among centers.

MeSH Keywords: Drug-Related Side Effects and Adverse Reactions • Liver Transplantation • Transplantation Tolerance

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Background

Long-term survival after liver transplantation (LT) has increased in recent decades, due to refinements in surgical technique and postoperative care, along with the availability of better anti-infectious and immunosuppressive (IS) drugs. However, IS drugs cause morbidity and mortality in LT recipients. Long-term mortality is mostly due to non-hepatic causes, and the risk of developing most of these non-hepatic conditions is increased by IS drugs [1–4]. Furthermore, the availability of highly efficacious drug combinations for the treatment of hepatitis C [5] will contribute to decreased deaths due to hepatic causes and reinforce the importance of non-hepatic causes of death.

IS minimization may overcome the adverse effects of IS drugs [6]. Many studies have evaluated the possibility of IS minimization, most of which have focused on the reduction or withdrawal of calcineurin inhibitors (CNI) in patients with nephrotoxicity [7,8]; however, the use of minimization in clinical practice is unreported.

The aim of this study was to provide an overview of the use of minimization in Spain through a cross-sectional, multicenter study. We also reviewed the indications of IS minimization and its effect on renal function. Our hypotheses were: a) that a high proportion of patients received minimized immunosuppression in the long term, b) that minimized patients had more co-morbidities than non-minimized patients, and c) that minimization benefitted these patients.

Material and Methods

We performed a cross-sectional study at 7 Spanish LT centers. From February 2014 to September 2014, approximately 100 non-selected consecutive LT recipients attending their regular outpatient follow-up were included in each center.

The inclusion criteria were as follows: a) age greater 18 years; b) time since transplantation more than 12 months (with no maximum limit); c) absence of recent acute complications; and d) written informed consent. The exclusion criteria were as follows: a) transplantation of any non-hepatic organ; b) liver retransplantation; c) hospital admission in the last month; and d) current or recent (less than 3 months) treatment of hepatitis C with an interferon-containing regimen.

The following data were recorded:

- Pre-LT data: demographic data, data about their liver disease and co-morbidities.
- Data about current status: results of the most recent laboratory tests, IS, and current information about graft function and co-morbidities.
- Data about IS therapy and renal function during the first post-LT year.
- Data about IS minimization and its indication.

Definitions

- IS minimization: steroid- and CNI-free IS or steroid-free and CNI-based IS, with tacrolimus levels below 5 ng/mL or cyclosporine levels were below 50 ng/mL [9,10]. These results required confirmation on at least 3 occasions over a minimum period of 6 months.
- Arterial hypertension: blood pressure above 140/90 mmHg (130/80 in diabetics) [11] or the need for pharmacological therapy to adequately control blood pressure.
- Diabetes: serum fasting glucose level above 126 mg/dL at least twice, or glycated hemoglobin above 6.5%, or serum glucose above 200 mg/dL 2 hours after an oral glucose tolerance test [12], or the need for anti-diabetic treatment.
- Dyslipidemia: serum fasting cholesterol levels above 250 mg/dL, or triglycerides above 150 mg/dL, or the need for pharmacological therapy.
- Pre-transplant renal dysfunction: serum creatinine level above 1.5 mg/dL. After transplantation, the glomerular filtration rate (GFR) was estimated using the MDRD4 formula [13], and the renal disease stages were assessed according to the chronic kidney disease (CKD) stages suggested by the NICE according to the GFR, expressed in mL/min/1.73 m^2 (stage 1: ≥90; stage 2: 60–89; stage 3A: 45–59; stage 3B: 30–44; stage 4: 15–29; stage 5 <15) [14].
- Smoking: cumulative smoking greater than 10 pack-years (obtained by the product of the number of 20-cigarette packs smoked daily and the number of years of smoking).

Statistical analysis

Quantitative variables are expressed as the means (standard deviation) if they were normally distributed, or medians (interquartile range) when they were not. Categorical variables are expressed as numbers (percentage). The following variables were studied as potentially associated with minimization: transplantation center, time since transplantation, age sex, indication for transplantation (hepatitis C, alcoholic liver disease, hepatocellular carcinoma), MELD score at transplantation, pre- and post-transplant renal dysfunction, arterial hypertension, cardiovascular disease, smoking, and diabetes mellitus. Chi-squared and Mann-Whitney U tests were used for univariate analysis. Variables with P <0.2 in univariate analysis were entered into a multivariate logistic regression analysis. Differences between different measures of the same parameter were analyzed by the Friedman test and, if they differed significantly between 2 consecutive time points, were compared using the Wilcoxon test.

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Table 1. General characteristics of the 661 patients participating in the study.

	Whole group		Minimized		No-minimized	
At the time of transplantation						
Age (years)	54	(48–60)	56	(49–60.5)	51	(46–59)
Sex						
Male	475	(72%)	259	(73%)	216	(70%)
Female	186	(28%)	94	(27%)	92	(30%)
Indication for transplantation						
Cirrhosis	619	(94%)	335	(95%)	284	(92%)
Hepatocellular carcinoma	204	(31%)	118	(33%)	86	(28%)
Alcoholic cirrhosis	330	(50%)	195	(55%)	135	(44%)
Hepatitis C	172	(26%)	84	(24%)	88	(29%)
MELD score	16	(13–20)	16	(12–20)	16	(13–19)
Renal dysfunction	67	(10%)	46	(13%)	21	(7%)
Arterial hypertension	109	(16%)	68	(19%)	41	(13%)
Cardiovascular disease	37	(6%)	22	(6%)	15	(5%)
Smoking	295	(45%)	168	(48%)	127	(41%)
Diabetes mellitus	133	(20%)	84	(24%)	49	(16%)
At the time of study (most recent follow-up)						
Time since transplantation (months)	101	(54–156)	107	(57–156)	91	(47–160)
Renal dysfunction	121	(18%)	87	(25%)	34	(11%)
Arterial hypertension	401	(61%)	227	(64%)	174	(56%)
Cardiovascular disease	118	(18%)	74	(21%)	44	(14%)
Smoking	103	(16%)	60	(17%)	43	(14%)
Diabetes mellitus	292	(44%)	162	(46%)	130	(42%)
Immunosuppression minimization	353	(53%)				
Unsuccessful minimization	80	(12%)				

Data are expressed as the median (inter-quartile range) or n (%).

Values reaching a P value less than 0.05 were considered statistically significant. The statistical analysis was performed with the SPSS package version 22.0.

The study protocol was revised by the Spanish Drug Agency (AEMPS). The Institutional Review Boards from all the participating centers approved the protocol. All participants provided written informed consent.

Results

Description of the population

We recruited 661 patients. The number of patients recruited in each center ranged between 70 and 106. Their general characteristics are presented in Table 1. Basal IS and its evolution are shown in Figures 1 and 2.

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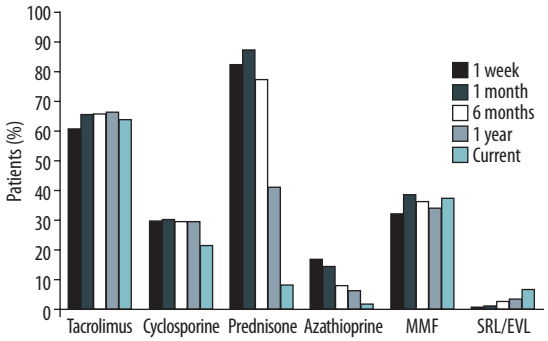

Figure 1. Immunosuppressive drugs used by the 663 patients participating in the study (data expressed as percentages). MMF – mycophenolate mofetil; SRL/EVL – sirolimus or everolimus.

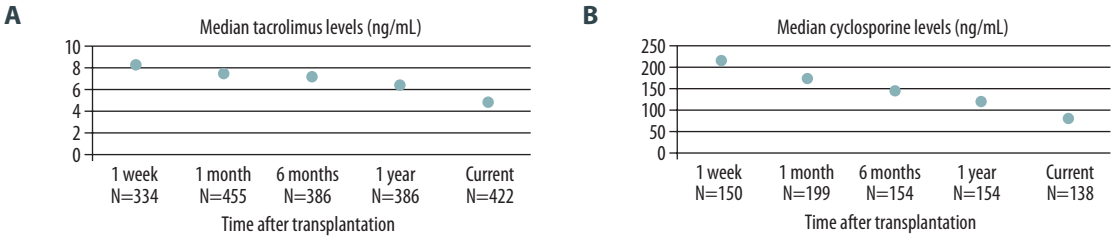

Figure 2. Evolution of the median levels of tacrolimus (**A**) and cyclosporine (**B**) in the 663 patients participating in the study.

IS minimization

Minimized IS was received by 353 patients (53.4%). Their current IS regimen is shown in Table 2. Comparison of the CNI levels between minimized and non-minimized patients is shown in Figure 3. Eighty-nine of the IS-minimized patients (13.4% of the global series) were free of CNI. The median time from LT to minimization was 32 (14–66) months. The time between minimization until the last follow-up in patients with minimized IS was 54 (25-99) months. The main indication for minimization was renal dysfunction (49.3%). Other frequent indications were high cardiovascular risk (19.3%), *de novo* malignancy (7.9%), cardiovascular disease (7.4%), and participation in a clinical trial (1.7%). Ninety-six patients (27.2% of minimized patients) were minimized without previous complications of IS therapy. The period between transplantation and minimization was shorter in patients with high cardiovascular risk (29 [12–56] months) and cardiovascular disease (36 [18–73] months) than in patients with renal dysfunction (43 [17–73] months), and *de novo* neoplasia (51 [24–66] months), and highest for patients in clinical trials (84 [27–101] months). Minimization was unsuccessfully attempted in 80 patients (12.1%) because of graft dysfunction.

Factors associated with minimization are shown in Tables 3 and 4 (showing only variables included in multivariate analysis). Minimization was significantly more frequent in older patients, and in patients with a longer post-transplant follow-up, and with pre- and post-transplant renal dysfunction.

Table 2. Current immunosuppression regimen in 353 liver transplant patients with minimized immunosuppression.

Tacrolimus-based	221
Tacrolimus monotherapy	117
Tacrolimus + Azathioprine	1
Tacrolimus + MMF	84
Tacrolimus + mTORi	18
Tacrolimus + MMF + mTORi	1
Cyclosporine-based	43
Cyclosporine monotherapy	18
Cyclosporine + MMF	22
Cyclosporine + mTORi	3
Free of calcineurin inhibitors	89
Azathioprine	1
MMF	52
mTORi	13
MMF + mTORi	6
Free of immunosuppression	17

MMF – mycophenolate mofetil; mTORi – mammalian target of rapamycin inhibitors.

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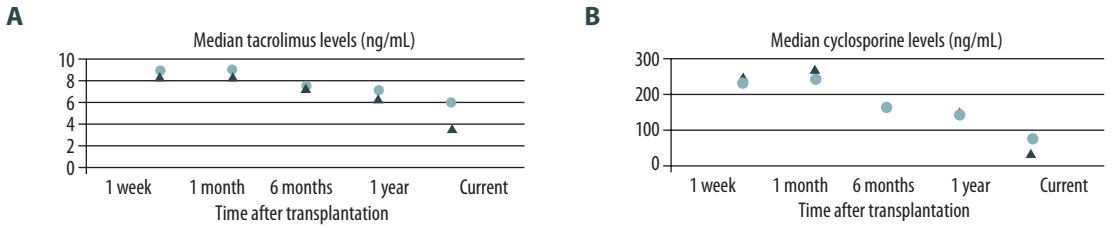

Figure 3. Comparison between the median levels of tacrolimus (**A**) and cyclosporine (**B**) levels in patients with minimized (triangles) versus non-minimized (circles) immunosuppression at the last follow-up.

Table 3. Factors associated with the minimization of immunosuppression (only variables entered into multivariate analysis; variables with P<0.2 are shown).

Factor	Percentage	P
Hospital A B C D E F G	 48% 70% 53% 55% 64% 49% 35%	<0.001
Age at transplantation (years)*	Minimization: 56 (49–60.5) No minimization: 51 (46-59)	<0.001
Time since transplantation (months)*	Minimization: 107 (57–156) No minimization: 91 (47–160)	0.11
Hepatitis C	Yes: 49% No: 55%	0.18
Alcoholic liver disease	Yes: 59% No: 47%	0.004
Hepatocellular carcinoma	Yes: 58% No: 51%	0.13
Smoking	Yes: 57% No: 50%	0.12
Pre-transplant renal dysfunction	Yes: 69% No: 52%	0.01
Pre-transplant arterial hypertension	Yes: 62% No: 52%	0.046
Pre-transplant diabetes	Yes: 63% No: 51%	0.015
Current renal dysfunction	Yes: 72% No: 49%	<0.001
Current arterial hypertension	Yes: 57% No: 48%	0.04
Cardiovascular complications	Yes: 63% No: 51%	0.03

Data are expressed as the proportion of patients on minimized immunosuppression for those fulfilling/not fulfilling the factor, except * median (interquartile range).

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Table 4. Factors associated with the minimization of immunosuppression (multivariate analysis).

Factor	OR (95% CI)		P
Hospital			
A	1.62	(0.88–3.02)	0.12
B	5.63	(2.97–10.66)	<0.001
C	1.90	(0.95–3.82)	0.07
D	2.81	(1.49–5.31)	0.001
E	3.79	(1.98–7.26)	<0.001
F	1.90	(1.02–3.54)	0.04
G (reference)	1		
Age at LT (years)	1.024	(1.004–1.044)	0.017
Time since transplantation (months)	1.004	(1.001–1.007)	0.009
Hepatitis C	0.96	(0.64–1.43)	0.83
Alcoholic cirrhosis	1.31	(0.88–1.95)	0.16
HCC	1.31	(0.88–1.95)	0.18
Smoking	1.06	(0.77–1.53)	0.76
Pre-transplant renal dysfunction	2.27	(1.23–4.18)	0.009
Pre-transplant arterial hypertension	1.19	(0.72–1.96)	0.51
Pre-transplant diabetes	1.30	(0.77–2.18)	0.32
Current renal dysfunction	2.70	(1.63–4.44)	<0.001
Current arterial hypertension	0.93	(0.63–1.37)	0.72
Cardiovascular complications	1.04	(0.65–1.67)	0.87

OR (95% CI) – odds ratio with 95% confidence interval; HCC – hepatocellular carcinoma.

A hospital effect was also found: the proportion of patients with IS minimization was significantly higher in some centers. The proportion of minimized patients in each hospital ranged between 35.3% and 70.2%.

Evolution of renal function

The evolution of GFR and CKD stages are shown in Figures 4 and 5. GFR decreased significantly after LT (Friedman test, P<0.001). Whereas this worsening of renal function was significant in the first 6 months; subsequent stabilization of renal function ensued 1 year after LT and at the most recent follow-up.

Renal function was compared among 3 different groups: patients without IS minimization, patients with minimization for renal dysfunction, and patients minimized for other causes. The evolution of GFR in these 3 groups is shown in Figure 6. Non-minimized patients had a significant decrease in the first 6 months and between the end of the first year and the last follow-up (Figure 6A). In patients minimized for renal dysfunction, GFR decreased gradually until the first year, remaining stable at the last follow-up (Figure 6C); whereas in patients minimized for other reasons, GFR stabilized after initially worsening and improved at the most recent follow-up (Figure 6B).

In patients who were minimized for renal dysfunction, the serum creatinine levels significantly decreased from 1.5 (1.3–1.8) mg/dL before minimization to 1.3 (1.1–1.7) at the most recent follow-up (P=0.004). To evaluate whether both early and late minimization were equally followed by improved renal function, we compared 2 subgroups (according to the date of minimization before or after the median of 43 months since LT). The serum creatinine levels decreased both in patients minimized for renal dysfunction before 43 months (before minimization: 1.4 (1.2–1.7) mg/dL; most recent: 1.3 [1.1–1.7] mg/dL; P=0.048) and in patients minimized after 43 months (before minimization: 1.5 [1.3–1.8] mg/dL; after minimization: 1.4 [1.1–1.8] mg/dL; P=0.02). The evolutions of the serum creatinine levels and GFR in patients minimized for renal dysfunction before or after 43 months are shown in Supplementary figures 1 and 2, respectively.

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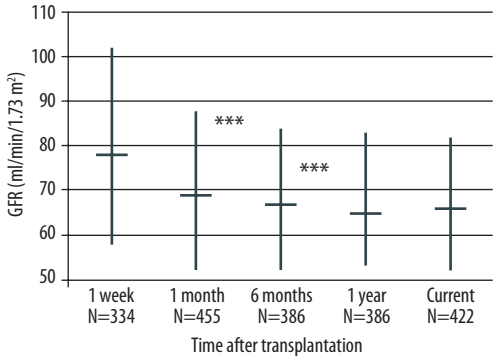

Figure 4. Evolution of the glomerular filtration rate (GFR) of the 663 patients participating in the study. Data are expressed as the median (interquartile range). Differences between 2 consecutive time points are expressed by the following annotation: *** P<0.001.

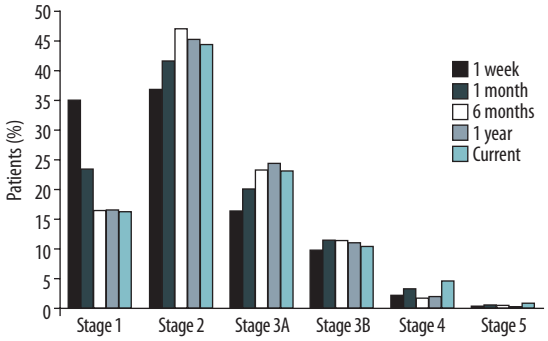

Figure 5. Evolution of the renal function of the 661 patients participating in the study according to the stages of chronic kidney disease (CKD).

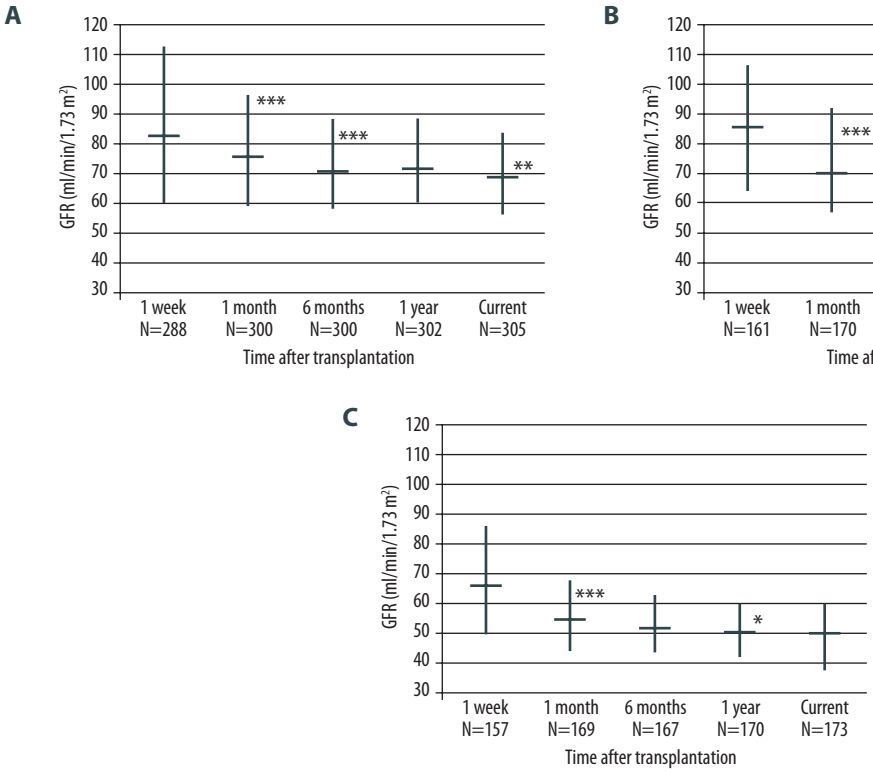

Figure 6. Evolution of glomerular filtration rate (GFR) of the patients with non-minimized immunosuppression (**A**), patients with minimized immunosuppression for non-renal causes (**B**) and patients minimized for renal dysfunction (**C**). Data are expressed as the median (interquartile range). Differences between 2 consecutive time points are expressed by the following annotations: * P value between 0.5 and 0.01; ** P value between 0.01 and 0.001; *** P<0.001.

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Calcineurin inhibitor-free patients

Eighty-nine patients (13.4% of the whole series) were free of CNI. Most of them were receiving MMF (52) or an mTORi (Table 2). Their median age was 57 (50.5–60.5) years and they had been transplanted a median of 127 (84–178.5) months prior. The main indications for minimization in these patients were renal dysfunction (58.4%), cardiovascular risk (26.9%), *de novo* neoplasia (13.5%), cardiovascular disease (6.7%), and participation in a clinical trial (3.3%). Seven patients were free of CNI without previous complications of IS therapy.

Substantial variability was observed in the proportion of patients that were free of CNI among the 7 centers: although the median was 14%, it ranged between 1% and 36%. No correlation was observed between the proportion of minimized patients in each hospital and the proportion of patients free of CNI.

As in the global minimization group, CNI withdrawal was followed by a significant improvement in renal function. The serum creatinine levels decreased from 1.6 (1.4–1.8) mg/dL before minimization to 1.3 (1.1–1.6) mg/dL at the last follow-up (P=0.002).

Discussion

Whereas CNI are the cornerstone of IS in all solid organ transplant programs, they are also responsible for much of the long-term morbidity and mortality. They cause dose-dependent nephrotoxicity [15], with high CNI exposure increasing the risk of *de novo* malignancy [16,17] or recurrent hepatocellular carcinoma [18,19]. Thus, the reduction or withdrawal of CNI may theoretically reduce the risk of most IS-related complications. In this study, we examined the IS minimization frequency in the real world. Thus, it reflects the status of IS in different hospitals with different IS protocols that have evolved over the years.

We found that more than 50% of unselected LT recipients were receiving an IS regimen with tacrolimus levels below 5 ng/mL, cyclosporine levels below 50 ng/mL or without any calcineurin inhibitor at a median of 32 months after LT. This finding contrasts with the maintenance IS used in other solid organ transplant recipients. For example, in a recent multicenter French trial of IS minimization in renal transplant recipients, the mean cyclosporine levels were above 100 ng/mL [20]. The proportion of patients receiving minimized IS was comparable to that in other series of LT [9], and higher than that in other series [10]. In the present study, the minimized IS proportion also varied among different centers, ranging from 35% to 70%. In fact, as this was a retrospective study, the center where the patients were followed was independently related to a higher proportion of minimization, and more than one-quarter of the patients were minimized without any previous complication of IS. When we analyzed the proportion of patients in whom minimization was attempted (successfully or unsuccessfully), the proportion ranged between 43% and 93% (median 66%). Thus, although minimization is attempted in most patients, a substantial range was observed among the different institutions. Another noteworthy finding was that more than 10% of the patients were free of CNI, despite the wide variability in these data. The proportion of patients free of CNI reached 36% in one of the centers participating in the study.

In this series, the most frequent indication for IS minimization was renal dysfunction. Minimization was followed by a significant improvement in renal function in patients who were minimized because of renal dysfunction. Long-term improvement of renal function was also found in patients minimized for other indications, whereas non-minimized patients experienced a decrease in GFR in the long-term. This finding suggests that IS minimization may help preserve renal function, including in patients lacking notable renal dysfunction, whereas a maintained standard IS leads to gradual worsening of renal function. This beneficial effect of minimizing (or even withdrawing) CNI has been found previously in other studies [21–25]. In the present study, the beneficial effect of minimization was evident both in patients minimized early and late; however, early intervention appears more effective in preserving renal function after LT [24]. Thus, early detection and intervention has been suggested regarding the progressive deterioration of renal function [26]. In this study, although renal function was worse in patients with minimized IS, the differences in the CNI levels during the first post-LT year were small. This finding suggests that in actual practice, IS minimization is usually delayed.

The second main indication for IS minimization was cardiovascular complications or a high risk thereof. The proportion of patients with risk factors for cardiovascular complications was high: 61% had arterial hypertension, 44% had diabetes mellitus, and more than 15% were smokers and had renal dysfunction. Consequently, 18% of the patients had cardiovascular complications. Because these cardiovascular risk factors are related to IS, changes in IS could be introduced to improve this risk profile. Steroid-free immunosuppression is associated with a lower proportion of diabetes mellitus and lower cholesterol levels [27]. Reducing or withdrawing CNI has been associated not only with improvement in renal function but also with better control of arterial hypertension, dyslipidemia, and diabetes mellitus [7,22,28,29]. However, the potential effect of IS minimization was not analyzed in this study. Accordingly, older patients and patients with diabetes mellitus accounted for a significant proportion of those who underwent IS minimization.

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CNI were successfully minimized in more than 50% of the patients, although minimization was not always possible. Eighty patients (12%) could not achieve IS minimization. This proportion is similar to that in previous studies [7,8,30]. Hence, the potential benefit of IS minimization should be balanced by the potential risk of rejection. Not all LT recipients can experience the potential benefits of IS minimization. Interestingly, the proportion of patients in whom minimization was unsuccessfully attempted ranged between 2% and 29% among the 7 institutions participating in this study.

The optimal IS minimization strategy requires further investigation. In a recently published systematic review of renal transplantation, the combination of low-dose CNI and mycophenolic acid formulations resulted in improved renal function and reduced risk of harm [31]. Conversion, withdrawal and avoidance of CNI were associated with fewer benefits and greater harms. Considering that LT has an immunological privilege over kidney transplantation, this finding may not be true for LT.

The main limitation of this study is its retrospective nature: our study shows that a large proportion of patients maintain adequate graft function; however, the proportion of patients who develop rejection on minimized IS is unknown. Whereas IS minimization was unsuccessfully attempted in 12% of the patients in the present series, some patients who may have died or lost their grafts would not have been detected because of the study design. By contrast, patients who might have been minimized successfully may have died before minimization was attempted because such patients tend to have more morbidities. Rather than attempting to evaluate a single minimization protocol, this study instead examined the use of minimization in a large cohort of patients.

Conclusions

More than 50% of LT recipients can achieve IS minimization in the long-term. The proportion of patients who could undergo minimization or perhaps CNI withdrawal might be higher, because the proportion of IS-minimized patients differs widely among hospitals. The main indication for IS minimization is renal dysfunction, and minimization may improve renal function. The potential benefits of IS minimization should be explored in future prospective trials, comparing the outcomes of patients who undergo minimization with the evolution of patients who maintain standard IS.

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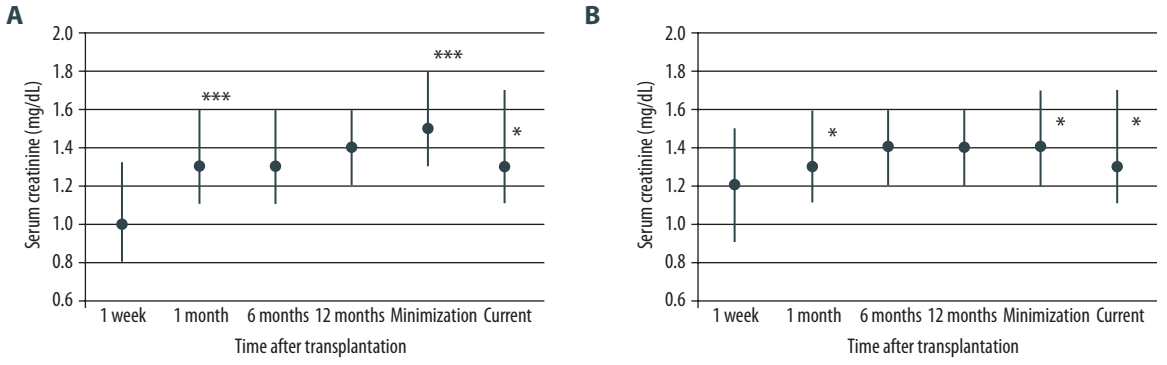
Supplementary Figures



Supplementary Figure 1. Evolution of the serum creatinine levels of the patients minimized for renal dysfunction after (**A**) or before (**B**) 43 months after transplantation. Data are expressed as the median (interquartile range). Differences between 2 consecutive time points are expressed by the following annotations: * P value between 0.5 and 0.01; ** P value between 0.01 and 0.001; *** P<0.001.

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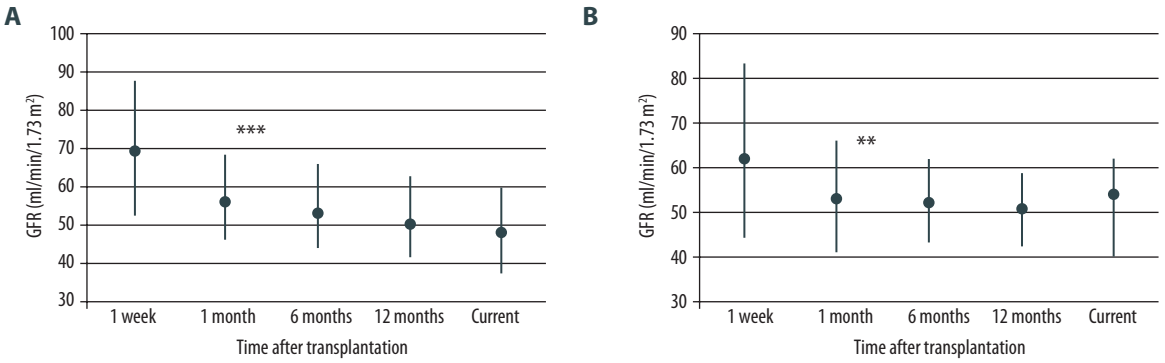

Supplementary Figure 2. Evolution of the glomerular filtration rate of the patients minimized for renal dysfunction after (**A**) or before (**B**) 43 months after transplantation. Data are expressed as the median (interquartile range). Differences between 2 consecutive time points are expressed by the following annotations: * P value between 0.5 and 0.01; ** P value between 0.01 and 0.001; *** P<0.001.

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