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Tacrolimus Formulations in De Novo Kidney Transplantation: Evidence from a Paired Kidney Study.

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To the Editor:

Tacrolimus is the cornerstone of immunosuppressive therapy in kidney transplantation, but its pharmacokinetic variability and narrow therapeutic window present challenges for optimal dosing and long-term graft survival[1]. Extended-release formulations, such as LCPT (Envarsus®) and ER-Tac (Advagraf®), have been developed to improve adherence and bioavailability [2][3]. However, direct comparative studies using paired kidneys from the same donor are scarce. Here, we present a prospective, paired, open-label study comparing the efficacy and safety of LCPT and ER-Tac in de novo kidney transplant recipients.

Methods

We included 108 adult recipients of deceased donor kidney transplantation (DDKT) at a single center (Málaga, Spain). Each donor provided kidneys to two recipients, one assigned to LCPT and the other to ER-Tac, minimizing donor-related confounding. All patients received standard triple immunosuppression (tacrolimus, mycophenolic acid, steroids). Clinical and laboratory data were collected at baseline and regular intervals up to 48 weeks. Renal function, acute rejection (clinical and subclinical), pharmacokinetics, and safety (including infection and post-transplant diabetes) were assessed. Protocol biopsies were performed at three months in a subset of patients.

Results

a) Baseline Characteristics:

Both groups were well matched for recipient and donor demographics (Table 1).

b) Renal Function:

Mean serum creatinine and estimated glomerular filtration rate (eGFR) were similar between groups throughout follow-up. At week 4, eGFR was 45 mL/min/1.73 m² (LCPT) vs. 41 mL/min/1.73 m² (ER-Tac; p=0.256); at week 48, 49 vs. 51 mL/min/1.73 m² (p=0.638).

c) Acute Rejection:

Clinical acute rejection occurred in 23.4% (LCPT) vs. 28.3% (ER-Tac; p=0.817). Subclinical rejection on protocol biopsy was observed in 61% (LCPT) vs. 80% (ER-Tac; p=0.405).

d) Pharmacokinetics:

LCPT required significantly lower total daily doses (TDD) than ER-Tac at all time points (week 48: 0.05 vs. 0.08 mg/kg; p=0.006). LCPT achieved higher trough concentrations early post-transplant (days 2 and 7; p=0.007 and p=0.04, respectively), with higher bioavailability (Figure 1).

Safety:

Incidence of post-transplant diabetes was 27.8% (LCPT) vs. 35.2% (ER-Tac; p=0.407). Rates of CMV and BK virus infection were numerically lower in the LCPT group. Patient and graft survival were comparable.

Discussion

Our paired-kidney analysis demonstrates that LCPT offers significant pharmacokinetic advantages over ER-Tac, with lower required doses and higher early bioavailability, while

maintaining similar efficacy and safety. These findings are consistent with previous studies showing improved bioavailability and reduced dose requirements with LCPT [4-6]. The observed trend toward reduced subclinical rejection and improved early renal function with LCPT may be clinically relevant, given the association of early subclinical inflammation with long-term graft loss [7][8].

Both formulations were well tolerated, with similar rates of adverse events. The lower infection rates and numerically reduced post-transplant diabetes in the LCPT group align with the hypothesis that improved pharmacokinetics may translate into fewer complications [9].

Limitations include the single-center design and limited sample size for protocol biopsies. Nonetheless, the paired-kidney methodology strengthens the comparative analysis by minimizing donor variability.

Conclusion

LCPT provides superior pharmacokinetic properties with a lower daily dose and higher early bioavailability compared to ER-Tac, without compromising efficacy or safety. Larger, multicenter studies are warranted to confirm these findings and evaluate long-term outcomes.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by de Provincial Ethics and Clinical Research Committee of Malaga (Cei Provincial de Malaga) (protocol code: 11/2017/PI13 and date of approval: 28 November 2017).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Date are available on request due to privacy restrictions. The data presented in this study are available on request from the corresponding author. In compliance with Spanish Organic Law 15/1999, the data are not publicly available.

Conflicts of Interest: The authors declare no conflicts of interest.

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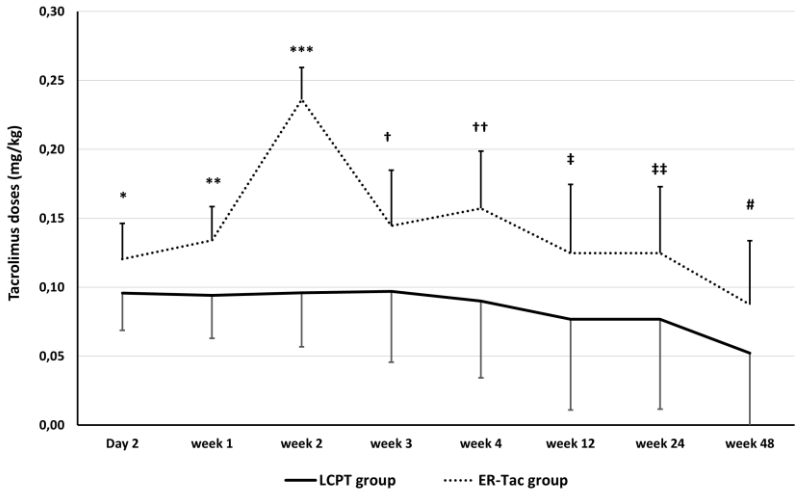
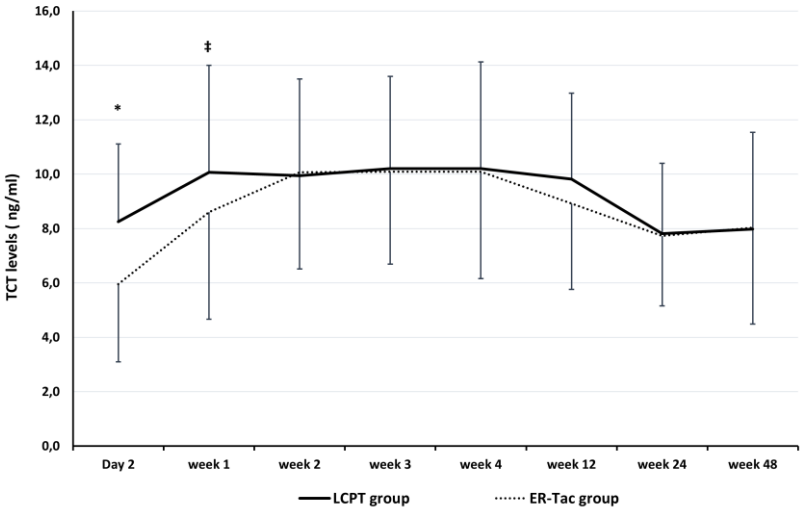
Table 1. Basal donors and recipients' characteristics.

	LCPT group (n= 54)	ER-Tac group (n= 54)	P value
Recipient characteristics			
Age, ys.	58±11	55±12	0.325
Sex (female), n, (%)	18 (33)	27 (50)	0.118
Race, n, (%)			
Caucasian	49 (90.7)	48 (88.9)	
Black	1 (1.9)	2 (3.7)	0.842
Arabic	4 (7.4)	4 (7.4)	
Pre-Tx diabetes n, (%)	13 (24)	8 (14)	0.184
Retransplant n, (%)	8 (14)	8 (14)	1
cPRA >50% n, (%)	10 (18)	9 (16)	0.801
Induction n, (%)			
No	4 (7.4)	7 (13)	
ATG	24 (44.5)	27 (50)	0.409
Basiliximab	26 (48.1)	20 (37)	
DGF n, (%)	16 (29)	18 (33)	0.775
CIT, hours	13.2±4.0	12.9±3.9	0.760
CMV Status of the recipient n, (%)			
CMV-negative	7 (13)	12 (22,2)	
CMV-positive	43 (79.6)	42 (77.8)	0.062
CMV-unknown	4 (7.4)	0 (0)	
Number of Incompatibilities (A-B-C-DR-DQ)	6.8±2.0	6.7±1.7	0.971
Donor characteristics			
Age, ys.	58±11	58±11	1
Sex (female) n, (%)	17 (31)	17 (31)	1
Diabetes mellitus n, (%)	4 (7)	4 (7)	1
Hypertension n, (%)	22 (40)	22 (40)	1
Creatinine, mg/dl	0.7±0.3	0.7±0.3	1
Stroke death n, (%)	29 (53)	29 (53)	1
CMV Status of the donors n, (%)			
CMV-negative	7(13)	7(13)	
CMV-positive	37 (68.5)	37 (68.5)	1
CMV-unknown	10 (18.5)	10 (18.5)	

Data are shown as mean and standard deviation or median and interquartile range.
Abbreviations: cPRA, calculated panel reactive antibody; ATG, anti-thymocyte globulin; DG, delayed graft function; CIT, cold ischemia time.


Tacrolimus doses (mg/kg)
0,30
0,25
0,20
0,15
0,10
0,05
0,00
*
**
***
†
††
‡
‡‡
#
Day 2
week 1
week 2
week 3
week 4
week 12
week 24
week 48
LCPT group
ER-Tac group


TCT levels (ng/ml)
16,0
14,0
12,0
10,0
8,0
6,0
4,0
2,0
0,0
*
‡
Day 2
week 1
week 2
week 3
week 4
week 12
week 24
week 48
LCPT group
ER-Tac group

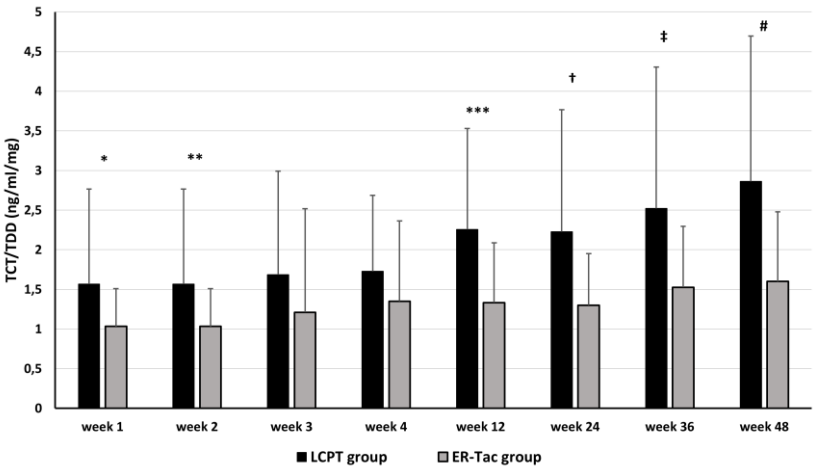


Figure 1. A) Tacrolimus TDD. Symbols indicating statistically significant differences between groups: *: p=<0.001; **: p<0.001; ***: p<0.001 ;†: p<0.001; ††; p<0.001 ; ‡; p<0.001 ; ‡‡; p=0.01 ; #; p= 0.006. B) Trough concentration of tacrolimus. Symbols indicating statistically significant differences between groups: *; p= 0.007; ‡; p=0.04. C) Bioavailability of Tacrolimus. Symbols indicating statistically significant differences between groups: *: p= 0.006; **: p=0.005; ***: p= 0.001; †: p=0.001; ‡; p= 0.001; #; p= 0.001.

The data are showed as mean ± standart desviation.

Abbreviations: TCT: Trough concentration of tacrolimus; TDD: total daily dose.