TITLE:Real-world bioequivalence of prolonged release formulation of Tacrolimus in renal transplant recipients.

The objective of this study is to determine whether the prolonged-release capsule formulation of tacrolimus, Conferoport® is bioequivalent to Advagraf® and Tacforius® in real world, according to the paramethers of EMA: maximun concentration(C_{max})(0,8- 1,2) and area under curve (AUC).(0,9- 1,10).

Disclosure

Lectures for Chiesi,Sandoz,Sanofi , Nordes and Astellas.

Material and methods I

We designed 2 prospective observational studies with 2 cohorts in each study.

In the first study recipients with Advagraf(R) were switched to Conferoport and

in the second from Conferoport to Tacforius.

We enroled first renal transplant recipients over 18 years transplanted from deceased donors at least two years in advance.

Patients had stable renal function with tacrolimus without change in dose the last six months.

They had no specific antibodies nor gastrointestinal disorders.

All recipients received a second immunosuppressant, without prednisone.

The pharmacokinetic parameters of each cohort were studied separately and were carried out in the two periods evaluated: Period 1(treated with the reference drug) and Period 2 (after conversion to the other drug).

Material and methods II

Patients received the same once-daily dose of both formulations in each of the two studies, with a time of 14 days between them.

Drug administration was on an empty stomach. Samples were taken in troughs (prior to the dose) and at 2 and 3 hours after administration.

Tacrolimus concentration was determined in blood by enzyme immunoassay (Dimension®, Siemens) (range: 1.2-30 ng/ml).

On each cohort, the end points were the pharmacokinetic parameter AUC from time zero to the trough concentration before next dose and C_{max} from administration of study drug.

Pharmacokinetic AUCs were calculated using the sampling time points and a logarithmic trapezoidal method.

Results

- A total of 41 patients were enroled (study 1 n=21, study 2 n=20), the average time since receiving transplant was 81.1 months.
- The mean dose of tacrolimus was 2.4 mg/24h. Baseline demographics, renal function and tacrolimus concentrations are showed in table 1
- The generic/generic ratios Advagraf of the parameters to assess bioequivalence (AUC and C_{max}) were within the ratio required by the EMA and are shown in table 2 .
- No side effects were observed during the study.

Table 1: Baseline demographics, renal function and tacrolimus concentrations

Patient's Characteristics	Cohort A-C		Cohort C-T	
	Period 1 (Advagraf®) Count (%) / Median (IQR)	Period 2 (Conferoport®) Count (%) / Median (IQR)	Period 1 (Conferoport®) Count (%) / Median (IQR)	Period 2 (Tacforius®) Count (%) / Median (IQR)
Patients	20	20	21	21
Age (yr)	60.1 (53.4 – 69.6)	60.1 (53.4 – 69.6)		
Sex, male, n (%)	16 (80 %)	16 (80 %)		
Weight (kg)	77.3 (66.8 – 90.5)	77.3 (66.8 – 90.5)		
BMI (kg/m²)	25.7 (22.9 – 29.2)	25.7 (22.9 – 29.2)		
Creatinine (mg/dL)	1.71 (1.18 – 1.85)	1.61 (1.14 – 1.62)	1.48 (1.11 – 1.65)	1.49 (1.14 – 1.57)
GFR (mL/min)	50.7 (36.7 – 64.3)	55.4 (41.5 – 73.4)	57.2 (38.9 – 74)	56.3 (39.3 – 75.5)
Hematocrit (%)	41.8 (37.7 – 46.2)	41.7 (37.1 – 47.1)	43.1 (38.9 – 45.8)	42.7 (38.6 – 45.2)
Dose (mg/day)	2.4 (1.8 – 3.1)	2.4 (1.8 – 3.1)	2.4 (2 – 3)	2.4 (2 – 3)
C_0 (mg/L)	4.69 (3.75 – 5.55)	4.54 (3.9 – 5.4)	4.0 (3.5 – 4.7)	3.9 (3.4 – 4.6)
C_2 (mg/L)	8.06 (6.85 – 9.7)	8.64 (7.05 – 10.35)	7.9 (6.3 – 9.2)	7.7 (6.5 – 8.6)
C_3 (mg/L)	8.03 (7.15 – 9.5)	8.21 (7.23 – 9.25)	7.1 (6.9 – 7.8)	7.3 (6.5 – 8.1)

IQR: Interquartil Range, BMI: Body Mass Index, GFR: Glomerular Filtration Rate

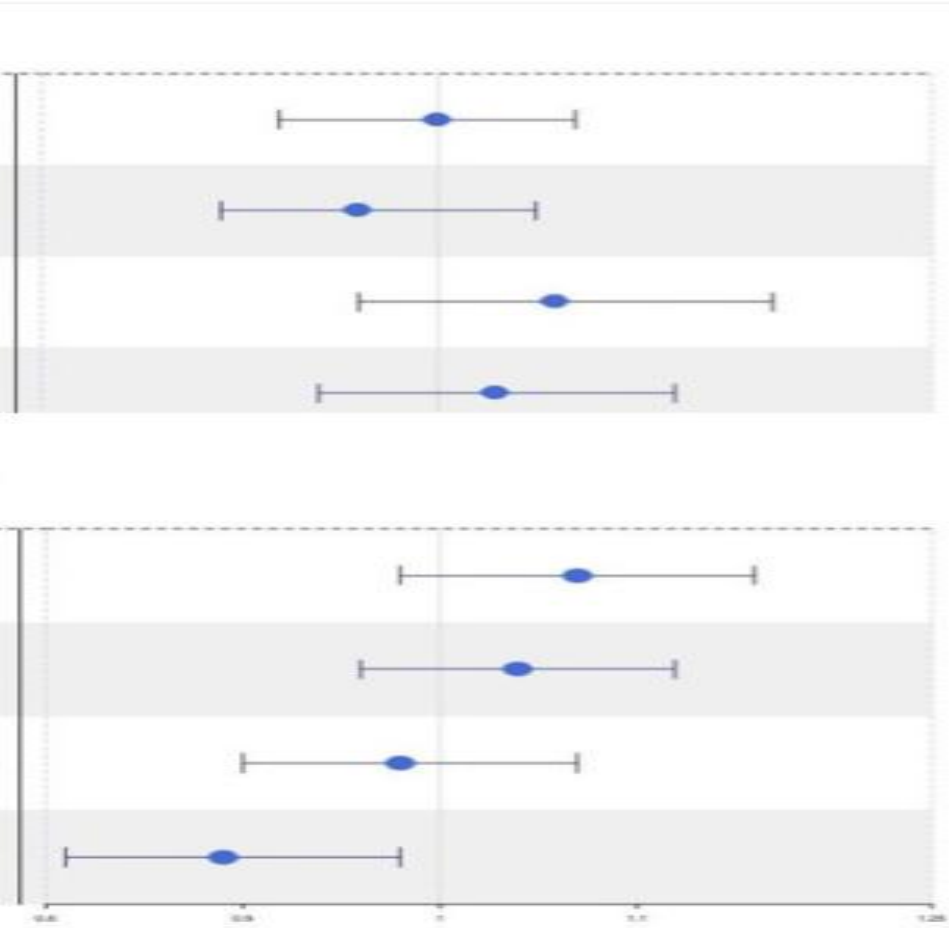
C0:trough level.C2:2hours after dose.C3:3hours after dose.

Table 2: parameters to assess bioequivalence

Area under curve(AUC),time 0,2,3(T0,T2,T3)

Study	Advagraf	Conferoport	Ratio
AUC	154	154.8	0.995
T0	4.69	4.54	0.963
T2	8.14	8.64	1.06
T3	8.03	8.21	1.028

Study	Conferoport	Tacforius	Ratio
AUC	146.8	136.2	1.066
T0	3.975	4.03	1.038
T2	7.935	7.895	0.982
T3	8.105	7.095	0.889



CONCLUSION

We confirm that in stable renal transplant recipients in the real-world, the extended-release Conferoport® is bioequivalent to the Advagraf® and Tacforius . Then ,they can be swithed without performing trough concentrations.