Pharmacokinetic Evaluation of Astagraf XL® and Prograf® in Renal Transplant Candidates Following Laparoscopic Sleeve Gastrectomy.

Diwan TS[1*], Leino AD[1*], Lichvar AB[1*], Vinks AA[2], Christians U[4], Shields AR[1,3], Cardi MA[3], Fukuda T[2], Mizuno T[2], Kaiser TE[1], Woodle ES[1], Alloway RR[1].

[1]Department of Surgery, Division of Transplantation, University of Cincinnati School of Medicine, Cincinnati, OH; [2]Department of Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [3]The Christ Hospital, Cincinnati, OH; [4]Department of Anesthesiology, University of Colorado Health Sciences Center, Denver, CO; * = All three authors contributed equally to the work

Background

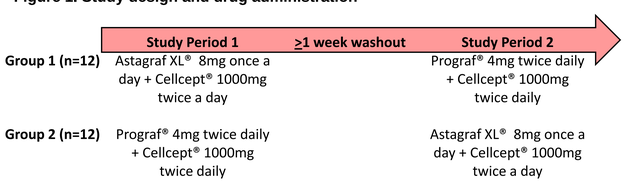
Severe obesity (BMI ≥ 35kg/m2) prevents access to renal transplantation (RTx). The Cincinnati Collaborative for Obesity Research (C_2ORE) study has shown Laproscopic Sleeve Gastrectomy (LSG) removes the obesity barrier to transplantation in most patients. Successful transplantation is linked to the ability to maintain therapeutic immunosuppressive blood levels. There is evidence that laparoscopic roux-en-Y gastric bypass (LRYGB) has adverse effects on the absorption of various immunosuppressants, requiring individualized dosing to achieve therapeutic levels. Alteration in gut anatomy results in changes impacting absorption, pre-systemic metabolism, and drug elimination mechanisms leading to variability in blood levels. Specific enzymes, such as CYP3A and P-glycoprotein (P-gp), are intimately involved in individual patient's ability to absorb immunosuppressive medications. These results quantitate the pharmacokinetic parameters of Prograf®, Astagraf®XL®, or Cellcept® post LSG.

Purpose: To describe the impact of LSG on the pharmacokinetics of Astagraf XL® and Prograf®

Methods

- Prospective, open-label, single-dose, cross-over pharmacokinetic study of Astagraf XL® and Prograf® in combination with Mycophenolate Mofetil (MMF, Cellcept®) in RTx candidates post-LSG.
- Patients were randomized in a 1:1 fashion to receive either Astagraf XL® or Prograf®. The statistician generated a randomization list using the SAS Proc PLAN (version 9.03).
- Inclusion criteria: adult (> 18 years) ESRD RTx candidate who were > 3 months post-LSG ; Exclusion criteria: allergies to any of the study medications, currently taking immunosuppressant medications, had post-surgical leak complications, or were taking any medications that interacted with tacrolimus.
- Pharmacokinetic blood samples were drawn over a 24-hour time period. Samples were drawn prior to dosing (C0) and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 12.5, 13, 14, 15, 16, 18, 20 and 24 hours post dosing (18 time points) at both study period 1 and 2.
- Samples were shipped to iC42 Clinical Research & Development (University of Colorado) to be analyzed via LC-MS/MS assay
- Selected SNPs were genotyped by a real-time TaqMan PCR with an appropriate variation step by direct sequencing. Phenotypes for CYP3A5, CYP3A4*22, and ABCB1 3435C>T were assessed in this study.

Figure 1. Study design and drug administration



Results

TABLE 1. Patient Demographics

Characteristic	n(%), (n = 23)
Male, n(%)	13 (56.5)
Mean Age, years (SD)	50.8 (11.4)
Race, n(%) Caucasian Black	 13 (56.5) 10 (43.5)
Hypertension, n(%)	21 (91.3)
Diabetes Mellitus– type 2, n(%)	10 (43.48)
Hemodialysis dependent, n(%)	20 (86.9)
Median time post-LGS, days (IQR)	449 (324 – 631)

FIGURE 2. Mean (SEM) tacrolimus concentration-time profiles of Prograf® and Astagraf XL® (A) and of 13-O-DMT (B)

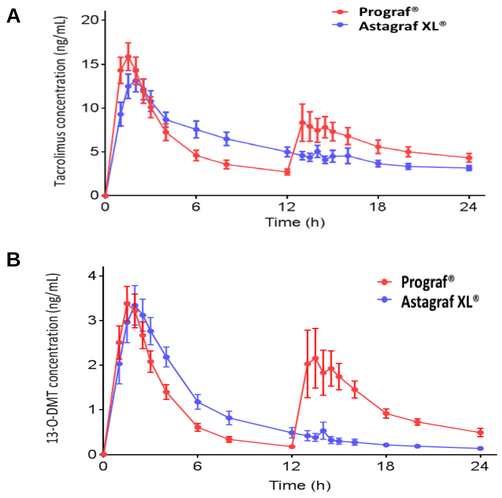


TABLE 2. Pharmacokinetic parameters of Prograf® and Astagraf XL® (A), and average bioequivalence parameters of tacrolimus products (B), and average bioequivalence of 13-O-desmethyl (C)

A

Parameter	Unit	Astagraf XL® (n=23)	Prograf® (n=23)	P-value
AUC_{0-24}	ng*h/mL	129.8 (34.3–292.7)	138.7 (26.5–356.2)	0.50
C_{max}	ng/mL	13.9 (6.0–31.0)	18.9 (4.0–35.2)	0.04
C_{min}	ng/mL	2.6 (0.7 – 6.27)	3.9 (1.5 – 10.7)	0.004
CL/F	L/h	61.62 (51.9 – 73.8)	57.7 (42.1 – 106.0)	0.879

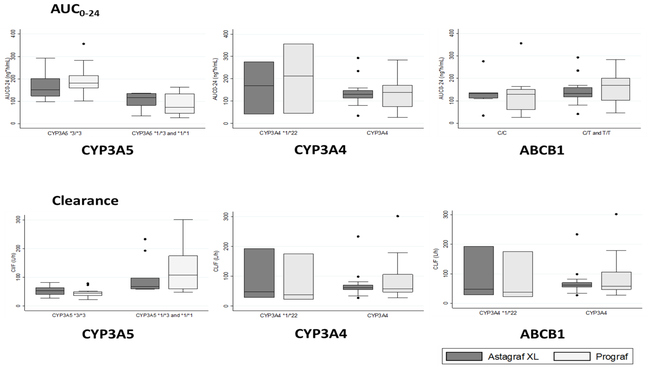
B

	Reference	Test formulation	Ratio of geometric means (%)	90% CI
AUC_{0-24}	Prograf®	Astagraf XL®	103.49	89.6 – 119.6
C_{max}	Prograf®	Astagraf XL®	92.53	80.45 – 106.43

C

Product	13-O-DMT AUC_{0-24} (ng*h/mL)	p-value
Prograf®	17.0 (6.6 – 59.9)	0.20
Astagraf XL®	20.2 (8.5 – 67.4)	

FIGURE 3. Pharmacokinetic comparison by CYP3A5, CYP3A4*22, and ABCB1 genotypes



Data are presented as box plots demonstrating medians and quartiles. Outliers are illustrated as plotted dots in the figure. CYP3A5*1 expressors had lower AUC0-24 (Prograf® p < 0.001; Astagraf XL® p = 0.008) and clearance (Prograf® p < 0.001; Astagraf XL® p = 0.008) values. All comparisons between CYP3A4 and ABCB1 were not statistically significant (p > 0.05).

TABLE 3. Multivariate analysis of factors influencing tacrolimus AUC by Astagraf XL® and Prograf®

Multiple Regression Model Astagraf XL® (R^2 = 0.62, p = 0.005)	Coefficient	SE	p-value
African American	78.60	30.28	0.020
Actual body weight	-0.94	0.57	0.116
CYP3A5*1	-130.53	31.94	0.001
CYP3A4*22	43.58	29.68	0.161
ABCB1 expressor	-39.71	25.99	0.146
Multiple Regression Model Prograf® (R^2 = 0.74, p < 0.001)	**Coefficient**	**SE**	**p-value**
Age	1.99	0.97	0.056
African American	42.38	33.96	0.230
CYP3A5*1	-167.61	33.48	< 0.001
CYP3A4*22	59.37	32.33	0.085
ABCB1 expressor	-75.69	27.86	0.015

Backward stepwise approach was used to assess the impact of actual body weight, race, age, CYP3A5*1 genotype, CYP3A4*22 genotype, and ABCB1 3435C>T genotype on tacrolimus AUC. Items were entered into the multivariate model if their p<0.20 in univariate modeling

Limitations

- Pre-transplant, ESRD population as opposed to a post-RT population
- Single-dose pharmacokinetics versus steady state pharmacokinetic analysis
- Not powered to detect differences in CYP3A4 or ABCB1 genotypes or to perform more complicated regression analyses on the different tacrolimus formulations.

Conclusion

Through this prospective study, we have demonstrated that LSG does not alter the absorption of Prograf®, Astagraf XL®, or Cellcept®. These findings are corroborated by simultaneous identification of specific genes know to affect immunosuppressant absorption, with the ability to determine the effects of these genes in the setting of LSG. Our recommendations are that no dose adjustments are required post-LSG for Prograf® or Astagraf XL®, only standard of care drug level monitoring.

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