Status of Generic Tacrolimus

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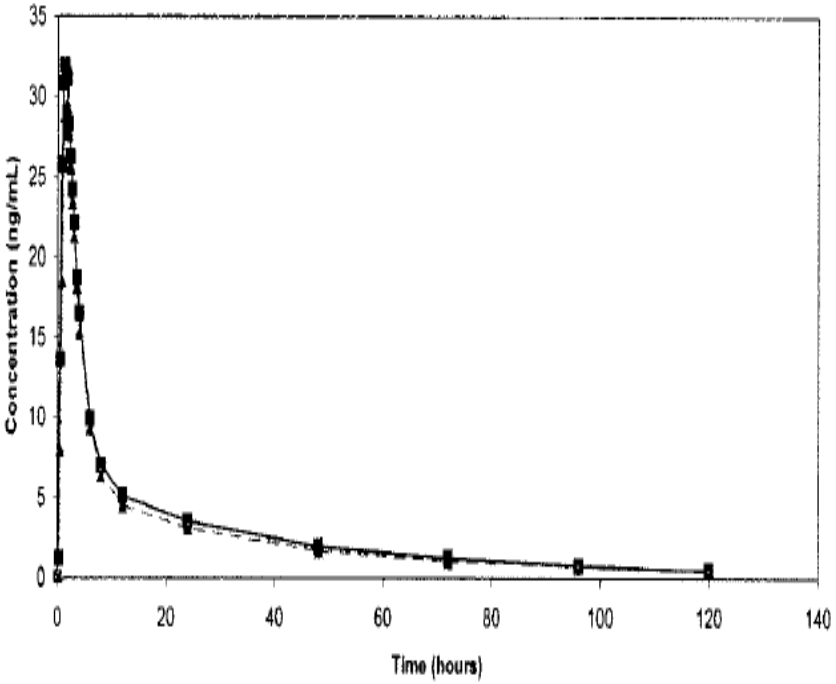
Arthur B. Straughn, Pharm.D
Professor Emeritus and
Director Drug Research Laboratory
University of Tennessee College of Pharmacy
astraughn@utmem.edu

Questions, answers to which, may be useful in future decisions

1. Is the currently approved generic version of Tacrolimus bioequivalent to Prograf?
2. Is the blood level variability seen in Tacrolimus related to the formulation?
3. What is the therapeutic range of Tacrolimus and is it an NTI drug?
4. What steps can be taken that would alleviate concerns as to the safety and efficacy of generic substitution?
5. Will a ruling limiting accessibility to an FDA approved generic version of Prograf protect patients from adverse therapeutic outcomes?

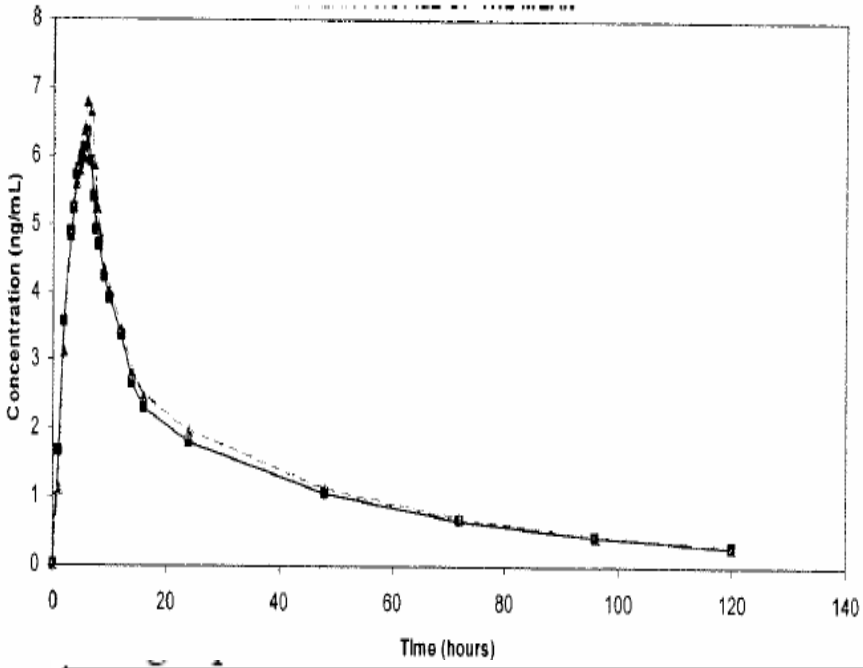
5 mg Generic Tacrolimus vs. 5mg Prograf

37 Subjects Fasting



Parameter	LSM ratio (90% confidence interval)
AUC0-t	110.7% (100.5-122.0%)
AUCinf	110.3% (100.3-121.3%)
Cmax	109.9% (101.8-118.6%)

39 Subjects Fed



Parameter	LSM ratio (90% confidence interval)
AUC0-t	96.1% (92.4-99.9%)
AUCinf	95.6% (92.0-99.3%)
Cmax	96.0% (90.1-102.3%)

Note: Prograf label is silent on dosage recommendation with food

True or False?

A highly variable, NTI drug would never meet regulatory standards for approval because neither safety nor efficacy could be proven. (Therapeutic Drug Monitoring would be useless)

FDA Advisory Committee for Pharmaceutical Science (4/14/04)

Bioequivalence of 1 and 5 mg tacrolimus capsules using a replicate study design

I Bekersky, D Dressler, W Colburn and Q Mekki

J. Clin. Pharmacol. 1999; 39; 1032

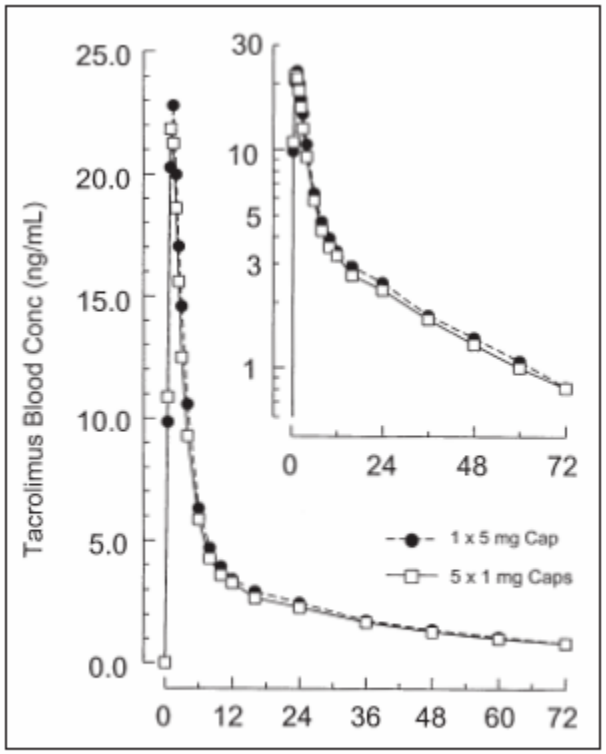


Figure 1. Mean tacrolimus blood concentration-time profiles (N = 29-32) in healthy male and female subjects receiving replicated doses of either 5 1 mg or 1 5 mg Prograf® capsules.

Mean Cp from 2 doses of A (1 x 5 mg) and 2 doses of B (5 x 1 mg)

Mean intrasubject %CV values ranged from 12.7% to 17.9% for treatments A_1 versus A_2 (N = 30) and 17.5% to 23.4% for B_1 versus B_2 (N = 29). Intersubject %CVs were calculated for the aforementioned parameter estimates across each treatment (A_1, A_2, B_1, and B_2) and ranged from 38.4% to 53.1%. Consequently, intersubject variability is approximately two to three times greater than intrasubject variability.

Within vs. Between Patient Variability in Bioavailability

Systemic absorption ranges from 5-93%.

Dosing conditions that may cause change in absorption

1. Food
2. Other Drugs
3. Concurrent Disease
4. Time of Dose (AM vs PM)
5. Compliance*

Conclusion:

Range in bioavailability reported for tacrolimus is between subjects and does not indicate wide variability within a subjects as long as dosing conditions remain constant.

*apparent change

Does Tacrolimus Exhibit Formulation Dependent BA ?

All drugs potentially have formulation dependent BA
(Reason there is a BA/BE Requirements for Drug Approval)

As shown, a high fat meal lowers both Cmax and AUC to the same extent for the generic formulation and innovator formulation.

Morning vs. Evening dosing of Prograf 5mg to fasted subjects resulted in a 60% decrease in Cmax with evening dosing and a 34% decrease in AUC. Is this due to the formulation or circadian changes in PK? Regardless, this large AM/PM difference is apparently of little clinical significance.

Conclusion:

Factors other than formulation are far more important to clinical success with Tacrolimus.

Is Tacrolimus an NTI drug?

Is minimum toxic Cp greater than 2 fold the minimum effective Cp?

1. There are no definitive publications defining TI of tacrolimus
2. Labeling (package insert) implies maintaining trough concentration in the following ranges are therapeutic:

   Adult Kidney: 5 to 20 ng/mL (4 fold)
   Adult Liver: 5 to 20 ng/mL (4 fold)
   Ped Liver: 5 to 20 ng/mL (4 fold)
   Adult Heart: 5 to 15 ng/mL (4 fold)

4. Peak to trough fluctuation over 12 hour dosing interval with IR formulations <u>much greater</u> than 2

Conclusion:

TI of tacrolimus not established, but what is known about the drug indicates it is greater than 2

CONCLUSIONS

The best way to ensure therapeutic success with tacrolimus is to monitor the patient closely and to encourage them to comply with dosage regimen instructions.

This will not be accomplished by limiting patient access to a generic tacrolimus formulation.

Bioequivalence and cGMP requires that any difference in the exposure of active drug to the patient (whether between brand and generic or lot to lot of brand) will be within medically accepted limits.