American Journal of Pharmacology and Toxicology 1 (3): 36-39, 2006
ISSN 1557-4962

Tacrolimus Dosing Challenges in an African American Child

[1]Teresa V. Lewis, [1]Tracy M. Hagemann and [2]Martin A. Turman
[1]College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA
[2]Department of Pediatrics, University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma, USA

Abstract: It has been suggested that African Americans have decreased effectiveness with immunosuppressive drugs. Data regarding the pharmacokinetics of tacrolimus in African Americans are limited. We present the case of an African American child in whom management of nephrotic syndrome caused by focal segmental glomerulosclerosis has been challenging due to unpredictable patient specific pharmacokinetic disposition of tacrolimus. Racial differences have been documented in literature to have an important impact on the pharmacokinetics and pharmacodynamics of certain drugs. As a result, African American patients may require larger doses or more frequent administration of certain medications to achieve therapeutic efficacy compared to Caucasians and other ethnic groups.

Key words: African American, FK506, pharmacokinetics, tacrolimus

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a disorder characterized by segmental glomerular scars involving some but not all glomeruli[1]. Patients will have proteinuria that is often nephrotic in presentation[2]. Other clinical features of FSGS include edema, hypertension, microscopic hematuria and renal insufficiency[1,2]. Tacrolimus is an immunosuppressive agent primarily used as prophylaxis therapy against acute rejection in liver and kidney transplant patients; however, it is also used in FSGS.

Treatment of FSGS is of the utmost importance. Failure to remit from nephrotic syndrome (NS) is associated with poor renal survival[3]. A review by Korbert *et al.*[4] reported 50% of nephrotic patients progressed to end-stage-renal failure after 6 to 8 years. Tacrolimus has been shown to be effective in achieving remission in individuals with refractory NS caused by FSGS. The drug's utility in FSGS is likely due to more potent cytokine suppression compared to cyclosporine[5]. Enhanced cytokine suppression may lead to more potent suppression of the circulating permeability factor that has been suspected in causing injury in FSGS[5,6]. Therapeutic efficacy of tacrolimus is determined via whole blood trough concentrations with targeted goal values of 4 to 7 ng mL^{-1}[7].

Ethnicity has been shown to impact clinical response to certain drug therapies. It has been suggested that African Americans see decreased effectiveness with immunosuppressive drugs. However, data regarding the pharmacokinetic disposition of drugs such as tacrolimus in this patient population is limited.

Case: We present the case of a 14 year-old African American female with a past medical history significant for nephrotic syndrome and persistent proteinuria. The child has had treatment resistant nephrotic syndrome since 4 years of age. Aggressive immunosuppressive therapies with cyclophosphamide, corticosteroids and cyclosporine have failed to induce remission in this patient. By 11 years of age she continued to have persistent problems with proteinuria. Laboratory examination at that juncture revealed the following results: serum total protein 4.7 g dL^{-1}; serum albumin 2.1 gm dL^{-1}; Blood urea nitrogen 6 mg dL^{-1}; serum creatinine 0.5 mg dL^{-1}; and urinary protein excretion 100 mg dL^{-1} with trace blood in her urine. A percutaneous renal biopsy revealed lesions characteristic of FSGS. This led to the decision to change her therapy. Cyclosporine was discontinued and she was weaned off prednisone. Tacrolimus monotherapy was initiated at 2 mg BID (0.03 mg kg^{-1} $dose^{-1}$; wt=60.3kg). The dose was adjusted to achieve targeted goal trough concentrations. Additional medications include lisinopril 2.5 mg BID (0.04 mg

Corresponding Author: Teresa V. Lewis, Pharm. D. The University of Oklahoma College of Pharmacy, Department of Pharmacy, Clinical and Administrative Sciences, P.O Box 26901, Oklahoma City, Oklahoma 73190-5040, Tel: 405-271-2859, Fax: 405-271-6430

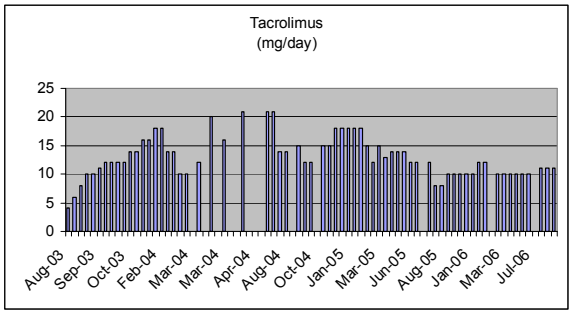
$kg^{-1}dose^{-1}$) for management of hypertension and furosemide 40 mg daily (0.66 mg $kg^{-1}dose^{-1}$) as needed for edema.

RESULTS AND DISCUSSION

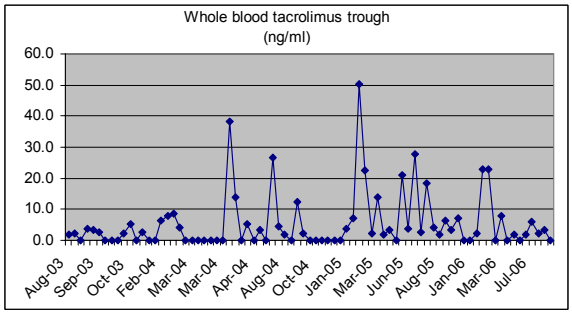
Over the past three years, she had been tried on 18 different variations in her tacrolimus dosing schedule. Her tacrolimus doses have ranged from 0.07 mg $kg^{-1}day^{-1}$ (wt: 60.3 kg) to 0.34 mg $kg^{-1}day^{-1}$ (wt: 62.4 kg) which was given in two to three divided doses (Fig. 1A). Routine monitoring of tacrolimus troughs were conducted monthly and weekly during some months. Occasionally, the patient's serum drug levels would rise without an identifiable cause to supratherapeutic concentrations becoming as high as 50.4 ng mL^{-1} (Fig. 1B). For the most part, her levels remained undectectable (< 1.5 ng mL^{-1}). Several attempts were made to chemically induce higher tacrolimus blood levels. Four days after starting erythromycin ethylsuccinate (EES), the patient's blood level went from undetectable to 6.5 ng mL^{-1}. The patient remained within therapeutic range for only two weeks. She again presented with undetectable levels despite increasing both tacrolimus and EES doses. EES was replaced by cimetidine which has remained on the patient's profile to the present. The child has had fewer undetectable levels with cimetidine; however, tacrolimus troughs remained unpredictable and her dose constantly requires adjustments.

Three times a day dosing of tacrolimus appears to be the better option for achieving therapeutic concentrations in this patient. On two separate occasions, a 2 hour post dose and a 6 hour post dose level were taken. The first evaluation was taken while the patient was receiving tacrolimus 6mg BID (0.09 mg $kg^{-1}dose^{-1}$; wt: 68.1 kg) which revealed the following results: 2 hour post dose level: 12.6 ng mL^{-1}; 6 hour post dose level: 6.6 ng mL^{-1}; calculated half-life of approximately 4 hours. The second assessment was performed when the patient was on tacrolimus 10 mg BID (0.16 mg $kg^{-1}dose^{-1}$; wt: 63.2 kg) and EES. This therapy revealed the following results: 2 hour post dose level: 38.4 ng mL^{-1}; 6 hour post dose level: 13.7 ng mL^{-1}. The estimated half-life was unexpectedly lower at 2.7 hours.

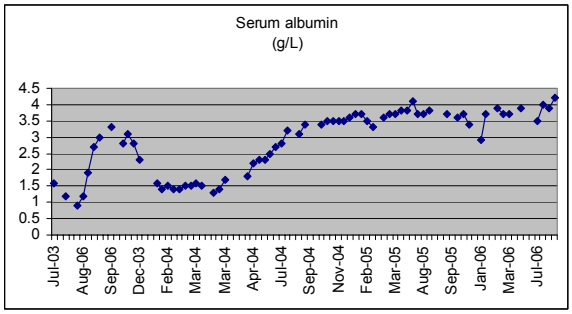
Throughout the duration of her treatment with tacrolimus, the patient did notice improvements in her serum albumin (Fig. 1C). Urine proteins were predominately found to be $\geq$ 300 mg dL^{-1}. Despite aggressive therapy and close clinical monitoring the patient has been able to achieve partial remission, but remains unremittent. Her most recent renal biopsy revealed only a single lesion with overall well preserved renal architecture. There was some focal atrophy but it was not extensive. Of important note was the fact that the patient did not appear to have



A. Tacrolimus dose at mg/day



B. Whole blood trough concentrations



C. Change in serum albumin with tacrolimus therapy

Fig. 1: The patient's clinical course during tacrolimus treatment

pathological findings indicative of toxicity associated with tacrolimus therapy.

Tacrolimus dosing adjustments in this patient have been quite challenging. The pharmacokinetic and pharmacodynamic dispositions of tacrolimus in this child have been erratic and unpredictable. The same dosing schedule did not always result in therapeutic drug concentrations. Dose increases did not always correlate with increased drug levels and paradoxically, decreases in dose sometimes led to exaggeratedly elevated trough drug levels. Additionally,

subtherapeutic troughs did not always correlate to clinical worsening as quantified by serum albumin assessments and proteinuria.

Tacrolimus is a macrolide lactone produced by *Streptomyces tsukubaensis*. Oral absorption in children is rapid, but erratic and incomplete with bioavailability being 10-52%[8,9]. Peak concentration following an oral dose is usually observed between 1-4 hours. Plasma protein binding of tacrolimus is approximately 99%. It binds mostly to α_1-acid glycoprotein but there is also some binding to albumin. The drug is extensively metabolized by the cytochrome P450 (CYP) system with the CYP3A pathway predominating. It is also subject to P-glycoprotein counter-transport. More than 95% of the drug is eliminated via biliary excretion and the elimination half-life ranges 3.5 to 40.5 hours (mean: 8.7 hours)[8,10].

Inter-individual variations to the immunosuppressive effects of tacrolimus may be due to extrinsic factors such as non-adherence to drug regimen, food-drug interactions, or drug-drug interactions. In our patient, non-adherence to therapy did not appear to be responsible for the variable tacrolimus levels. Food decreases the rate and extent of absorption with high fat meals producing the most pronounced effect and it is associated with a 35% reduction in AUC[8]. Concomitant administration of tacrolimus and certain foods such as grapefruit juice may result in inhibition of CYP3A mediated metabolism of tacrolimus. This may lead to elevated trough concentrations of the drug. Drugs that inhibit the CYP3A pathway could also lead to elevated troughs. In our patient we tried co-administrations of tacrolimus with erythromycin and tacrolimus with cimetidine to take advantage of this drug interaction. Drugs that induce CYP3A mediated metabolism of tacrolimus or drugs that compete with receptor binding sites may interfere with efficacy of tacrolimus. Our patient was not on any other agent that could have produced decreased efficacy of tacrolimus.

Pharmacokinetic differences: Intrinsic factors such as genetic polymorphisms of P-glycoprotein and of CYP3A expression has been postulated as contributing factors to the variable patient responses to tacrolimus treatment. Uesugi *et al.*[11] evaluated the relationship between tacrolimus dose and drug levels in relation to hepatic and intestinal expression of CYP3A5 in liver transplant patients. This study suggested that hepatic and intestinal CYP3A5 played an important role in the first pass effect of orally administered tacrolimus. Individuals who had the CYP3A5*1 allele expressed both hepatic and intestinal CYP3A5. These individuals had lower drug concentrations per dose ratio of tacrolimus compared to individuals with other CYP3A5 genotypes. Mancinelli *et al.*[12] demonstrated that African Americans exhibited significantly lower bioavailability and maximum blood concentrations with orally administered tacrolimus in a study that evaluated ethnicity and pharmacokinetics of intravenously and orally administered tacrolimus. The authors concluded that lower therapeutic efficacy of tacrolimus in African Americans were likely due to genetic polymorphisms of P-glycoprotein and CYP3A expression.

CONCLUSION

Several studies have evaluated the pharmacokinetic and pharmacogenomics of tacrolimus in adults, African Americans and in children; however, there have not been any studies evaluating tacrolimus disposition in African American children. The unpredictability in patient responses to the immunosuppressive effects of tacrolimus in African Americans may likely be caused by differences in oral absorption rather than drug clearance and tacrolimus pharmacogenomics may explain variability in tacrolimus disposition. African Americans may require larger doses or more frequent administration of tacrolimus to achieve therapeutic efficacy compared to Caucasians.

REFERENCES

1. Tucker, J.T, 2002. Focal segmental glomerulosclerosis in African Americans. Am. J. Med. Sci., 323: 90-3.
2. Korbert, S.M., 1999. Clinical picture and outcome of primary focal segmental glomerulosclerosis. Nephrol. Dial. Transplant., 14 (Suppl. 3): 68-73.
3. Hogg, R.J., R.J. Portman, D. Milliner, K.V. Lemley, A. Eddy and J. Ingelfinger, 2000. Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a pediatric nephrology panel established at the National Kidney Foundation conference on proteinuria, albuminuria, risk, assessment, detection and elimination (PARADE). Pediatrics, 105: 1242-9.
4. Korbert, S., M. Schwartz and E. Lewis, 1994. Primary focal segmental glomerulosclerosis: clinical course and response to therapy. Am. J. Kidney Dis., 23: 773-83.
5. Loeffler, K., M. Gowrishankar and V. Yiu, 2004. Tacrolimus therapy in pediatric patients with treatment-resistant nephrotic syndrome. Pediatr. Nephrol., 19: 281-7.

6. Vincenti, F. and G.M. Ghiggeri, 2005. New insights into the pathogenesis and the therapy of recurrent focal glomerulosclerosis. Am. J. Transplant., 5: 1179-85.
7. Duncan, N., A. Dhaygude, J. Owen, T.D. Cairns, M. Griffith, A.G. McLean, A. Palmer and D. Taube, 2004. Treatment of focal and segmental glomerulosclerosis in adults with tacrolimus monotherapy. Nephrol. Dial. Transplant., 19: 3062-7.
8. Product Information: PROGRAF® capsules, injection, tacrolimus capsules, injection. Astellas Pharma US, Inc., Deerfield, IL, 2005.
9. Schubert, M., R. Venkataramanan, D.W. Holt, L.M. Shaw, W. McGhee, J. Reyes, S. Webber and R. Sindhi, 2004. Pharmacokinetics of sirolimus and tacrolimus in pediatric transplant patients. Am. J. Transplant., 4: 767-73.
10. Staatz, C.E., C. Willis, P.J. Taylor and S.E. Tett, 2002. Population pharmacokinetics of tacrolimus in adult kidney transplant recipients. Clin. Pharmacol. Ther., 72: 660-9.
11. Uesugi, M., S. Masuda, T. Katsura, F. Oike, Y. Takada and K. Inui, 2006. Effect of intestinal CYP3A5 on postoperative tacrolimus trough levels in living-donor liver transplant recipients. Pharmacogenet. Genomics., 16: 119-27.
12. Mancinelli, L.M., L. Frassetto, L.C. Floren, D. Dressler, S. Carrier, I. Bekersky, L.Z. Benet and U. Christians, 2001. The pharmacokinetics and metabolic disposition of tacrolimus: a comparison across ethnic groups. Clin. Pharmacol. Ther., 69: 24-31.