The Value Of Tacrolimus Drug Levels In The Management Of Nephrotic Syndrome In Children

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Citation

Abstract

Background: Patients with nephrotic syndrome are treated initially with corticosteroids. Tacrolimus is an important alternative for children who have frequent relapses or who are resistant to steroids. The relationship between the tacrolimus level and drug efficacy is unknown in these circumstances. We conducted this retrospective review to determine this relationship in patients with minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS).Methods: A retrospective chart review was performed on patients diagnosed with MCNS or FSGS at Cohen Children's Medical Center who were treated with tacrolimus. Results: Seventeen patients with MCNS were identified, mean age 4.6±3.6 years, who were treated with tacrolimus for 36±28 months. No relationship between the initial drug level and time to remission was found. There was a direct correlation between the average tacrolimus level during treatment and the number of relapses per month (P < 0.02). Twelve patients with steroid resistant FSGS, mean age 9.0±5.5 years, received tacrolimus for 21±23 months. There was no relationship between paired levels of proteinuria and the trough tacrolimus concentration determined at the time of assessment of proteinuria. Conclusion: There is no dose response relationship to justify the use of higher tacrolimus dosages in the treatment of MCNS or FSGS.

INTRODUCTION

Pediatric patients with newly diagnosed nephrotic syndrome (NS) are given corticosteroids as a first line of treatment and in most cases the steroids are effective in inducing disease remission [1]. However, the vast majority of children subsequently have relapses and require repeated exposure to steroids to manage frequently relapsing or steroid-dependent NS [2]. This treatment can be associated with significant toxicity. In addition, approximately 10-20% of the patients with new-onset NS fail to respond to the initial course of corticosteroids and comprise the category of steroid-resistant NS [3]. This group of patients continues to pose a therapeutic challenge for pediatric nephrologists.

In the last 10-15 years, the prevailing practice among nephrologists has been to use the calcineurin inhibitor, cyclosporine, to treat frequently relapsing/steroid dependent or steroid resistant NS [4,5]. However, cyclosporine may not always be effective and there is a high likelihood of disease relapse after withdrawal of the drug. In addition, secondary cyclosporine resistance and nephrotoxicity are important complications associated with prolonged use of this treatment [4]. Because of these difficulties, there has been an ongoing search for alternative treatments, including other calcineurin inhibitors. Recently nephrologists have been prescribing tacrolimus to treat both categories of NS patients [6]. Uncontrolled studies have demonstrated the effectiveness of tacrolimus in patients with frequently relapsing/steroid-dependent and steroid-resistant NS [7-12]. However, the side effect profile of tacrolimus is similar to cyclosporine and its use is also limited because of nephrotoxicity.

The relationship between the prescribed tacrolimus dosage with regard to drug level and drug efficacy is unknown for patients with NS, regardless of whether the drug is used to minimize steroid exposure in frequently relapsing/steroid-dependent cases or to reduce proteinuria in patients with steroid-resistant disease. We conducted this retrospective study to determine this relationship by examining patients with minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS).

PATIENTS AND METHODS

Patients: This retrospective, single-center chart review was conducted in all pediatric patients who were treated with

tacrolimus (Prograf®) for either MCNS or FSGS, between 2003 and 2011, at Cohen Children's Medical Center. Patients were treated with corticosteroids in accord with ISKDC treatment guidelines [13]. Tacrolimus was prescribed in an initial dose of 0.05-0.1 mg/kg per day in two or three divided doses. A similar starting dose was utilized for patients with MCNS and FSGS. Clinical chemistry tests were done as indicated and were performed in the hospital core laboratory. Urinary protein excretion was expressed as the protein:creatinine ratio (mg:mg) in a first morning urine sample. Trough levels of tacrolimus (ng/mL) were measured after 1 week of therapy and at all subsequent clinical visits in samples drawn prior to the morning dose. The tacrolimus dosage was routinely lowered if the drug level was >10 ng/mL.

Patient charts were obtained from either active clinical files or off-site storage. The following data were extracted from the record of each MCNS patient: age, gender, height, weight, blood pressure, albumin, cholesterol, serum creatinine, estimated glomerular filtration rate (GFR_e), tacrolimus levels, time interval from the administering of tacrolimus to first remission, mean tacrolimus level, and the number of relapses per month during treatment. The following data were tabulated for each FSGS patient at each clinic visit: age, gender, height, weight, blood pressure, albumin, cholesterol, serum creatinine, GFR_e blood urea nitrogen, tacrolimus level, and urine protein: creatinine ratio (Up:cr).

Data are presented as mean ± SD. The differences between values were compared using the Student t-test. Relationships between variables were assessed by linear regression analysis. Results were considered statistically significant if the P value was less than 0.05.

This retrospective chart review was approved by the institutional Review Board.

RESULTS

MCNS patients: During the 8-year study period, 17 patients with MCNS, based on the presence of persistent steroid-responsive disease, were treated with tacrolimus. The demographic and laboratory features are summarized in Table 1. The majority was male and they all had a normal GFR_e (>90 ml/min/1.73 m^2) at the time tacrolimus was initiated. The total duration of treatment with tacrolimus was 36±28 months. The mean number of determinations of the trough tacrolimus level in each patient was 10.5±9.3. Among the patients with MCNS, 88% of the tacrolimus levels were

≤6 ng/mL

Tacrolimus was started together with daily corticosteroids in 16 out of the 17 patients while they were in relapse. In this group, the mean time interval between the initiation of tacrolimus and the onset of remission, defined as urine negative or trace for 3 consecutive days for dip stick testing, was 3.6±7.7 months. All of the patients went into remission after initiation of tacrolimus treatment; however, there was no relationship between the initial tacrolimus level and the time to remission (P=0.403). Unexpectedly, there was a direct relationship between the mean tacrolimus level during the treatment period and the number of relapses per month of treatment (P=0.013) (Figure 1). At the last follow-up, 5 patients were in extended remission on tacrolimus treatment alone and 12 patients continued to have relapses while receiving tacrolimus.

FSGS Patients: During the 6-year study period, 12 patients with biopsy-proven steroid resistant FSGS were treated with tacrolimus. The demographic and laboratory features are summarized in Table 2. At the last follow up, patients exhibited a mean serum creatinine of 0.7±0.5, a mean albumin of 3.6±0.9, and a GFR_e of 136±49. The mean Up:cr was 2.4±4.2.

Five patients were treated with an ACE and 1 patient was treated with both an ACE and ARB throughout the treatment period. One patient began treatment with an ACE but was later taken off the drug. Two patients were given an ACE in the middle of their treatment and 3 patients were not treated with an ACE or ARB. There was no relationship between use of an ACEI and/or ARB and the tacrolimus levels or the timing of remission. Blood pressure remained stable during the treatment period.

The mean duration of tacrolimus treatment was 21±23 months. In the FSGS cohort, 72% of the tacrolimus levels were ≤6 ng/mL. In an analysis of all time points in which there were paired measurements of proteinuria and the trough tacrolimus level (n=103, 9±5 per patient), there was no relationship between these two determinations (Figure 2). Similar to the patients with MCNS, there was no relationship between the initial tacrolimus level and the time to remission. When the relationship was examined for each patient individually, only two dose response curves showed a significant direct relationship between tacrolimus level and proteinuria. At the last follow-up visit, 4 patients were in complete remission (Up:cr <0.2), 6 patients were in partial remission (Up:cr 0.2-2), and 2 had persistent nephrotic-range

proteinuria (Up:cr >2).

Figure 1

Figure 1. Graph illustrating the relationship between mean tacrolimus level and the number of relapses per month (R^2 = 0.00299, P= 0.01).
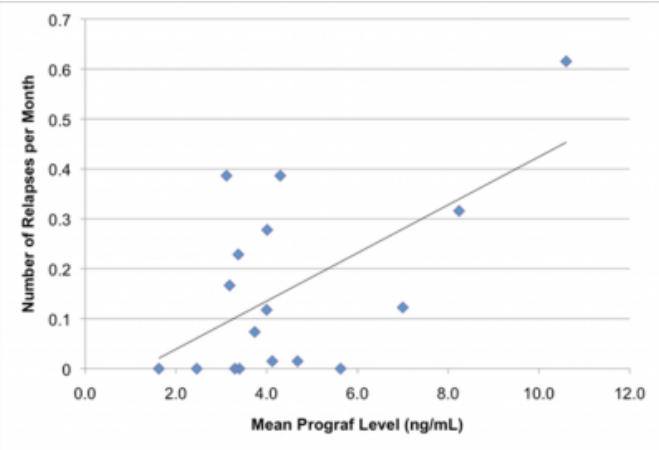

Figure 2

Figure 2. Graph illustrating the relationship between paired tacrolimus protein levels taken at the same time (R^2 = 0.34803, P= 0.58)
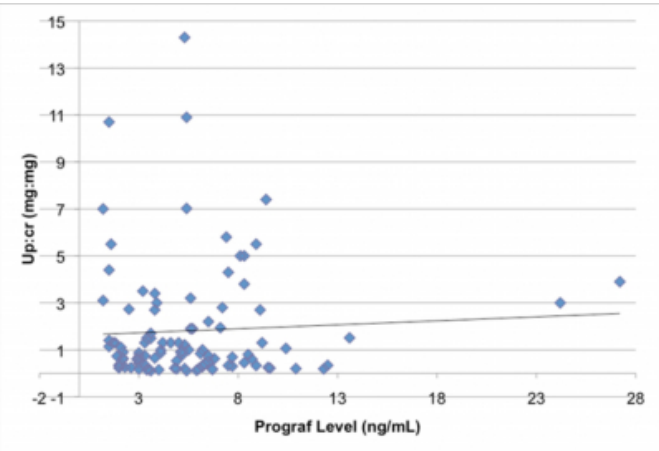

Figure 3

Table 1: Demographics and Laboratory Findings of Patients with MCNS (N=17)

Age (years)	4.6 ± 3.6
M: F	12:5
Height (cm)	125.2 ± 26.7
Weight (kg)	39.2 ± 25.1
Blood Pressure (mmHg)	105 ± 15/66 ± 13
Serum Creatinine (mg/dL)	0.4 ± 0.2
GFR$_e$ (ml/min/1.73 m^2)	182 ± 88
Albumin (g/dL)	3.1 ± 1.0
Cholesterol (mg/dL) (n=16)	324 ± 207
Initial Tacrolimus Dosage (mg/kg/day)	0.11 ± 0.04

Figure 4

Table 2: Demographics and Laboratory Findings of Patients with FSGS (N=12)

Age (years)	9.0 ± 5.5
M: F	10:2
Height (cm)	135.7 ± 36.4
Weight (kg)	49.3 ± 36.3
Blood Pressure (mmHg)	119 ± 19/73 ± 13
Serum Creatinine (mg/dL)	0.6 ± 0.4
GFR$_e$ (ml/min/1.73 m^2)	175 ± 74
Up:cr	4.6 ± 3.4
Albumin (g/dL)	2.3 ± 0.8
Cholesterol (mg/dL)	364 ± 166
Initial Tacrolimus Dosage (mg/kg/day)	0.11 ± 0.04

DISCUSSION

The calcineurin inhibitor, tacrolimus, is widely prescribed for children with nephrotic syndrome in two very distinct circumstances – in patients with steroid responsive disease who are experiencing intolerable side effects of corticosteroids and in patients with steroid resistant disease in order to achieve normalization of proteinuria and remission of the nephrotic syndrome. The precise mechanism of action of tacrolimus when it is used to treat the nephrotic syndrome is unclear. Traditionally, it was thought that tacrolimus acts on an immune target to lower the production of a molecules(s) that promote proteinuria. Recent data suggest that the calcineurin inhibitor, cyclosporine, reduces proteinuria by altering the actin cytoskeleton in the podocyte [13].

Regardless of its mechanism of action, there is no bioassay to assess the therapeutic efficacy of tacrolimus in pediatric patients with nephrotic syndrome. In the absence of such a definitive test, nephrologists monitor the tacrolimus trough level, primarily to prevent nephrotoxicity. The implicit assumption is that the drug level will correlate with drug efficacy in a direct linear manner. In fact, over a decade ago, it was proposed that increased binding of cyclosporine to serum lipids in children with NS would reduce the effective drug concentration and therefore, higher drug doses and higher levels would be required to achieve remission in proteinuria if a calcineurin inhibitor is prescribed [14]. However, this has never been systematically studied.

A review of the recent literature describing the use of tacrolimus for steroid–responsive and steroid-resistant nephrotic indicates that all of the reports detail the mean dose, trough level, and duration of treatment [6-12]. However, there is no comment on the relationship of outcome to the drug level achieved in the individual patient.

Prior to completing this retrospective review, we anticipated that higher trough levels of tacrolimus would be associated with better outcomes. Although the mean circulating tacrolimus concentration was in the therapeutic range in both patient groups (data not shown), we focused on the relationship between the drug level and therapeutic response for individual patients. Thus, we predicted that higher drug levels would lead to shorter times to remission and a lower relapse rate in children with steroid-responsive disease. In patients with steroid-resistant nephrotic syndrome, we predicted that there would be an inverse correlation between tacrolimus levels and proteinuria. Much to our surprise, in

the first group, we found that there was no relationship between tacrolimus levels and the time to remission. Moreover, the subsequent relapse rate was directly related to the tacrolimus level. It is important to note that tacrolimus was started while these patients were still in relapse. This contrasts with our use of mycophenolate mofetil, which is started after achieving remission in children with steroid-responsive NS. Similarly, in those with steroid-resistant disease, there was no overall inverse relationship between trough tacrolimus levels and proteinuria. In fact, there was a subset of patients in whom there was a significant direct relationship between the drug level and urinary protein excretion. Thus, based on our data, we propose that a target tacrolimus level cannot be defined that can predict which patients will achieve remission. Instead, a response to the calcineurin inhibitor can and does at much lower drug levels than those used in kidney transplant recipients and higher tacrolimus levels may only increase the risk of nephrotoxicity. We wish to point out that unlike the children with MCNS who were followed solely with dipstick testing, the efficacy of tacrolimus in the patients with FSGS was based on quantitative assessment of proteinuria. Our overall findings suggest that the patients with high tacrolimus levels are those in whom the clinical efficacy is diminished and the drug dose is steadily increased in the hope that the relapse rate or urinary protein excretion will decline.

Our data cannot shed light on the controversy regarding the mechanism of action of tacrolimus when it is used to treat nephrotic syndrome. However, our results suggest that there is a threshold pattern of response to the drug and that no further benefit is likely to accrue either in terms of relapse rate or reduction in proteinuria by targeting a tacrolimus trough level above 5-6 ng/mL. We base this recommendation on the observation that over 75% of patients in the two groups combined were ≤6 ng/mL.

We acknowledge the limitations of our retrospective study. The sample size is relatively small and the tacrolimus dosing schedule was not standardized. While the determinations of proteinuria were objective and accurate, there was no assessment of patient adherence to the treatment recommendation and this may have influenced the drug levels. Nonetheless the range was within expected limits and the dose range was not exceedingly wide suggesting that most of the children took the prescribed dose. Finally, our results do not have any bearing on the appropriate duration of tacrolimus therapy for either indication.

Based on our review, we would recommend that if

tacrolimus is used to treat children with nephrotic syndrome, steroid-responsive or steroid-resistant disease, the target trough level should not exceed 5-6 ng/mL. This will enable demonstration of therapeutic efficacy and minimize potential adverse effects of this calcineurin inhibitor, primarily nephrotoxicity (word count: 1941).

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