Calcineurin inhibitor induced nephrotoxicity in steroid resistant nephrotic syndrome

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ABSTRACT

Prolonged therapy with calcineurin inhibitors (CNI) is effective in patients with difficult nephrotic syndrome. However, information on prevalence and risk factors for nephrotoxicity in children with steroid-resistant nephrotic syndrome is limited. This retrospective observational study was conducted on 40 patients with steroid-resistant nephrotic syndrome treated with cyclosporine (CyA) ($n = 28$) or tacrolimus ($n = 12$) for more than 2 years. Nephrotoxicity was defined by the presence of striped fibrosis involving ≥10% of the interstitium or nodular hyalinosis in more than one arteriole. Ten additional parameters were graded semi-quantitatively. Continuous data are presented as median and interquartile range (IQR). The median (IQR) age at onset of nephrotic syndrome and CNI therapy were 30 (21-45) and 49.5 (40-102.5) months. A second renal biopsy, following 30 (26-35) months of CNI therapy, showed histological toxicity in 10 (25%) patients. Toxicity was seen in 7 and 3 patients receiving CyA and tacrolimus, respectively, and 5 patients each with minimal change and focal segmental glomerulosclerosis. Therapy with CNI was associated with significant increases in scores for global glomerulosclerosis, tubular atrophy, interstitial fibrosis, nonnodular arteriolar hyalinosis ($P < -0.001$ for all), arteriolar smooth-muscle vacuolization ($P = -0.02$), juxtaglomerular hyperplasia ($P = -0.002$), and tubular microcalcinosis ($P = -0.06$). Risk factors for nephrotoxicity were initial resistance (OR 9; 95% CI 1.0-80.1; $P = -0.049$); dose of CyA (OR 9.2; 95% CI 1.1-74.6; $P = -0.037$); duration of heavy proteinuria (OR 1.2; 95% CI 1.0-1.4; $P = -0.023$); and hypertension during therapy (OR 6; 95% CI 1.3-28.3; $P = -0.023$). Following prolonged CNI therapy, one in four biopsies show features of toxicity. Prolonged duration of heavy proteinuria, hypertension, initial steroid resistance and high CyA dose predict the occurrence of nephrotoxicity.

Key words: Cyclosporine, focal segmental glomerulosclerosis, tacrolimus

Introduction

The management of patients with steroid resistance, constituting 10-20% children with idiopathic nephrotic syndrome, is difficult.[1,2] Disease complications are common and patients with persistent proteinuria show progressive decline in renal function. The outcomes have improved following the use of calcineurin inhibitors (CNI), cyclosporine (CyA), or tacrolimus, which induce remission in 50-80% patients.[3,4] Prolonged treatment with CNI results in several adverse effects, the most significant being nephrotoxicity, characterized histologically by striped pattern of interstitial fibrosis, and peripheral nodular arteriolar hyalinosis.[5,6] Risk factors for nephrotoxicity include younger age,[7,8] prolonged duration of therapy,[8,9] high trough levels of medications,[7] persistent nephrotic range proteinuria[9] and hyperuricemia.[10] Most information pertains to CyA and there is limited information on tacrolimus or on comparative toxicities.

We reviewed the case notes of patients with steroid resistant nephrotic syndrome treated with tacrolimus or CyA for at least 2 years in order to determine renal histological changes associated with their use and for prevalence and risk factors for nephrotoxicity.

Materials and Methods

Medical records of all patients, 1- to 18-year-old, with idiopathic steroid resistant nephrotic syndrome secondary to minimal change disease (MCD) or focal segmental

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glomerulosclerosis (FSGS) who began treatment with either CyA or tacrolimus between January 2005 and December 2008, were reviewed. A repeat kidney biopsy to determine CNI nephrotoxicity was performed in all patients who had received therapy for 2 or more years. Standard definitions were used for nephrotic syndrome, remission, and relapse.[2] Initial steroid resistance was defined as the absence of remission despite treatment with prednisolone at a dose of 2 mg/kg/day for 4 weeks at the onset of disease; patients with initial remission but steroid resistance in a subsequent relapse were classified as late resistance.

Therapy

Therapy with CyA or tacrolimus was given at a dose of 4-5 and 0.1-0.15 mg/kg/day, respectively, in two divided doses. The trough levels were measured using radioimmunoassay for CyA and microparticle enzyme immunoassay for tacrolimus, targeted to 80-150 and 4-7 ng/ml, respectively; lower levels were accepted for patients in remission. All the patients received treatment with prednisolone (0.4-0.5 mg/kg on alternate days), enalapril (0.2-0.4 mg/kg/day), and calcium supplements. At 6 months, response to therapy with CNI was categorized as complete remission (urine protein to creatinine, Up/Uc ratio <0.2 mg/mg); partial remission (Up/Uc 0.2-2.0, normal serum albumin level and no edema); and non-response (Up/Uc ratio >2, edema or hypoalbuminemia).[2] Therapy with these agents was discontinued in patients with nonresponse at 6 months or persistently elevated serum creatinine ≥50% above baseline, hyperglycemia (glucose >180 mg/dl on two or more occasions), seizures, or recurrent and severe headaches.[2]

Relapses were treated with prednisolone at 2 mg/kg/day until remission, followed by 1.5 mg/kg on alternate days for 4 weeks with subsequent tapering. Duration of heavy proteinuria was the number of days of nephrotic range (3-4+) proteinuria, including the time to partial or complete remission and during disease relapses.

Renal histology

Renal biopsy was performed at initiation of therapy, and after 2 years of therapy. Specimens with seven or more glomeruli in at least one core were considered adequate, and examined by light microscopy (hematoxylin–eosin, periodic acid Schiff and silver methenamine stains) and immunofluorescence staining for immunoglobulins and complement. All biopsies were reviewed by two nephropathologists who were blinded to clinical details. Histology was classified as MCD or FSGS.[11]

Based on the second biopsy, nephrotoxicity was defined as the presence of either striped pattern of interstitial fibrosis and tubular atrophy involving at least 10% of the tubulointerstitium, or arteriolopathy characterized by nodular hyalinosis in more than one arteriole.[8-10,12] Additional parameters on both the biopsies were graded from 0 to 3, based on percent histological involvement, as proposed by Kambham *et al.*[13] Global glomerulosclerosis, mesangial matrix expansion, mesangial hypercellularity, isometric tubular vacuolization and tubular atrophy were scored as 0 (none), 1 (1-25%), 2 (26-50%), and 3 (>50% involved). Non-striped interstitial fibrosis was graded as 0 (0-5%), 1 (6-25%), 2 (26-50%), and 3 (>50% involved); and juxtaglomerular hyperplasia and tubular calcinosis as 0 (none), 1 (<10%), 2 (11-25%), and 3 (>25% involved). Non-nodular arteriolar hyalinosis and arteriolar smooth muscle vacuolization were scored as 1 (involving single arteriole), 2 (two arterioles involved), and 3 (many arterioles involved). A score of ≥2 was considered significant involvement for the purpose of analysis.

Analysis

Data were analyzed using Stata, version 11.1 (StataCorp, College Station, TX, USA). Continuous data are presented as median and interquartile range (IQR). Clinical and histological features among patients receiving CyA and tacrolimus, and those with presence or absence of CNI nephrotoxicity, were compared using the rank sum test. Within group comparisons were made using the sign rank test. Risk factors associated with CNI toxicity were examined by univariate logistic analysis and results are expressed as odds ratio (OR) with 95% confidence interval (CI).

Results

Of 40 patients, 28 had received therapy with CyA for 31 (26-35.5) months and 12 had received tacrolimus for 29 (27-30.5) months until the time of the second biopsy. The clinical and laboratory features at initiation of therapy were similar for the two groups [Table 1]. Initial and late steroid resistance was present in 24 and 16 patients, respectively. The renal histology at the onset of CNI therapy showed MCD and FSGS in 24 and 16 patients, respectively. FSGS showed tip and perihilar lesions in 1 patient each, and not otherwise specified histology in 14. The median (IQR) dose of CyA was 4.6 (4.1-5.1) mg/kg/day and tacrolimus was 0.11 (0.09-0.14) mg/kg/day. The respective trough levels at second biopsy were 145.8 (80.7-178.7) ng/ml and 6.08 (3.2-7.5) ng/ml.

At second biopsy, 9 patients treated with CyA had complete remission, 13 had steroid-sensitive relapses, and 6 had partial remission. Of the patients receiving tacrolimus, four had sustained remission, six had steroid

Table 1: Features at initiation of therapy with calcineurin inhibitors

	Total (*n*=40)	Cyclosporine (*n*=28)	Tacrolimus (*n*=12)
Boys	24 (60)	16 (57.1)	8 (66.7)
Initial resistance	24 (60)	17 (60.7)	7 (58.3)
Age at onset of disease, months	30 (21-45)	31.5 (22.5-43)	27.5 (19.5-54)
Age at therapy, months	49.5 (40-102.5)	48.5 (40-102.5)	55 (32.5-111)
Weight SDS	0.26 (-1.36 to 0.47)	-0.45 (-1.16 to -0.03)	0.49 (-1.55 to 0.96)
Height SDS	-1.32 (-2.49 to 0.25)	-1.5 (-2.61 to -0.1)	-0.19 (-1.9 to 1.6)
Hypertension	19 (47.5)	12 (42.9)	7 (58.3)
Serum creatinine, mg/dl	0.50 (0.30-0.65)	0.50 (0.30-0.70)	0.41 (0.40-0.60)
Estimated GFR, ml/min/1.73 m^2	90.8 (77.4-126.1)	90.8 (72.5-126.1)	94.1 (79.1-125.1)
Blood albumin, g/dl	2.3 (1.8-3.21)	2.1 (1.7-3.2)	2.7 (2.2-3.2)
Cholesterol, mg/dl	301 (215-465)	333 (229-466)*	237.5 (193-299)*
Initial biopsy			
Minimal change disease	24	17	7
Focal segmental glomerulosclerosis	16	11	5
Duration to second biopsy, months	30 (26-35)	31 (26-35.5)	29 (27-30.5)

*P<0.05, GFR: Glomerular filtration rate, GN: Glomerulonephritis, SDS: Standard deviation score, Data for continuous variables are presented as median (interquartile range) and for categorical variables as number (%)

sensitive relapses and two had partial remission.

Histopathology before and following therapy

Scores for histological variables on initial biopsies were comparable in patients receiving CyA and tacrolimus. At baseline, patients with FSGS showed slightly higher scores for mesangial matrix expansion (rank sum P = –0.079) and arteriolar smooth muscle vacuolization (P = –0.091).

Comparison of findings between biopsies performed before and following 30 (26-35) months of therapy showed increase in scores for global glomerulosclerosis (mean difference 0.52; 95% CI 0.25-0.79; P = 0.001), tubular atrophy (0.48; 95% CI 0.24-0.72; P < –0.001), interstitial fibrosis (0.6, 95% CI 0.31-0.89; P < –0.001), non-nodular arteriolar hyalinosis (0.92, 95% CI 0.51-1.33; P < –0.001), arteriolar smooth muscle vacuolization (0.48; 95% CI 0.08-0.88; P = –0.02), juxtaglomerular hyperplasia (0.72, 95% CI 0.28-1.16; P = –0.002), and tubular microcalcinosis (0.36, 95% CI -0.01-0.73; P = –0.06). Progression in these findings was similar for biopsies with MCD and FSGS, and for those receiving CyA or tacrolimus (data not shown).

Histological evidence of CNI toxicity was present in 10 (25%) biopsies. Striped interstitial fibrosis was present in nine patients and nodular arteriolar hyalinosis in three. A significant proportion of biopsies with nephrotoxicity also showed high (≥2) scores for nonstriped interstitial fibrosis and nonnodular arteriolar hyalinosis [Table 2].

Table 2: Number of biopsies (percentage) with semi-quantitative scores ≥2 for various histological variables in patients with or without calcineurin inhibitor nephrotoxicity

	No calcineurin inhibitor toxicity (*n*=30)	Calcineurin inhibitor toxicity (*n*=10)	*P**
Global sclerosis	3 (10)	3 (30)	0.15
Mesangial matrix expansion	1 (3.3)	0 (0)	0.99
Mesangial hypercellularity	6 (20)	1 (10)	0.66
Isometric vacuolization in tubules	0 (0)	0 (0)	0.99
Tubular atrophy	6 (20)	4 (40)	0.23
Non-striped interstitial fibrosis	4 (13.3)	6 (60)	0.007
Non-nodular arteriolar hyalinosis	6 (20)	8 (80)	0.001
Arteriolar smooth muscle vacuolization	7 (23.3)	3 (30)	0.69
Juxtaglomerular hyperplasia	10 (33.3)	2 (20)	0.69
Tubular microcalcinosis	4 (13.3)	3 (30)	0.34

*Chi square or Fisher exact test. Figures in parentheses are percentages

Risk factors for nephrotoxicity

Upon comparison of baseline features at the initiation of therapy, patients with nephrotoxicity showed higher frequency of initial resistance (9 of 10 vs. 15 of 30; P = 0.032) and hypertension (6 of 10 vs. 6 of 30; P = –0.04) than in those without nephrotoxicity. The duration of heavy proteinuria was significantly longer at 8.5 (4.9-28.1) weeks in patients with nephrotoxicity compared with 3.2 (0.9-8.0) weeks in those without toxicity (P = –0.007). The former patients had also received higher doses of cyclosporine [5.0 (4.8-5.1) mg/kg/day vs. 4.3 (3.9-4.8) mg/kg/day; P = –0.037]. On univariate analysis, factors associated with nephrotoxicity were initial resistance (OR 9; 95% CI 1.0-80.1; P = –0.049); dose of CyA (OR 9.2; 95% CI 1.1-74.6; P = –0.037); duration of heavy proteinuria (OR 1.2; 95% CI 1.0-1.4; P = –0.023) and hypertension during therapy (OR 6; 95% CI 1.3-28.3; P = –0.023).

Change in estimated glomerular filtration rate

Serum creatinine and estimated glomerular filtration rate at the initiation of therapy were 0.50 (0.30-0.65) mg/dl and 90.8 (77.4-126.1) ml/min/1.73 m^2, respectively [Table 1]. The GFR was similar for patients receiving CyA

and tacrolimus ($P = –0.77$), and for those with MCD and FSGS (85.1 vs. 112.7 ml/min/1.73 m^2; $P = –0.15$). At repeat biopsy, serum creatinine was 0.53 (0.30-0.91) mg/dl and GFR 81.0 (64.0-109.2) ml/min/1.73 m^2. The decline in GFR in patients with nephrotoxicity was 22.7 (−7.0 to 28.2) ml/min/1.73 m^2 compared with −1.8 (−22.4 to 39.8) ml/min/1.73 m^2 in those without toxicity ($P = –0.76$). The reduction in GFR was similar for patients receiving CyA and tacrolimus (7.4 vs. −3.2 ml/min/1.73 m^2; $P = –0.73$) and for MCD and FSGS (−1.8 vs. 22.7 ml/min/1.73 m^2; $P = –0.17$).

Other adverse effects

Patients treated with CyA showed gum hyperplasia ($n = –7$) and hirsutism ($n = –8$). Seizures, raised transaminases and hyperlipidemia were observed with tacrolimus and CyA in one patient each. Hyperglycemia ($n = –2$) resolved upon discontinuation of tacrolimus. There was no correlation between renal and extra renal toxicities.

Discussion

Our results show that 25% patients of steroid resistant nephrotic syndrome treated with CyA or tacrolimus for 2-3 years have histological evidence of nephrotoxicity. The prevalence was similar for both agents and for patients with MCD and FSGS. Risk factors for toxicity were initial resistance to corticosteroids, higher dosage of CyA, presence of hypertension during therapy and prolonged duration of nephrotic range proteinuria.

Nephrotoxicity associated with use of CNI is defined variably based on a spectrum of histological abnormalities.[7,12,14-16] On the basis of current criteria, the prevalence of nephrotoxicity in children treated with CyA for nephrotic syndrome varies, and relates to the duration of therapy. Histological features of toxicity were noted in 3.8% of the patients following 12-month therapy, and 15.4-16.7% after treatment for 12-41 months.[14,15,17] The high prevalence (25%) in the present study may reflect a sampling error or referral bias at a tertiary center. Iijima *et al.* and Fujinaga *et al.* proposed that treatment with CyA for more than 2 and 3 years, respectively, was an independent risk factor for nephrotoxicity.[8,9] Others suggest that nephrotoxicity is related to high doses of CyA, or to high blood levels of tacrolimus.[7,14] These findings confirm the experience in transplant recipients relating nephrotoxicity to the dose and duration of CyA therapy.[18,19] Although experimental evidence suggests that angiotensin-converting enzyme inhibitors might have a role in preventing interstitial fibrosis,[20] further studies are necessary to examine their role in preventing CNI-associated nephrotoxicity.

The presence of nephrotic range proteinuria has been associated with CyA-induced nephrotoxicity. Nephrotoxicity was related to the frequency of disease relapses in 30 patients with difficult nephrotic syndromes.[8] Similar to our findings, Iijima *et al.* showed that heavy proteinuria lasting for over 30 days was an independent predictor of CyA-associated nephrotoxicity.[9] Other risk factors for nephrotoxicity in the present patients were hypertension during therapy and initial corticosteroid resistance. A previous report on 53 patients with nephrotic syndrome showed that treatment for hypertension was associated with CyA-associated nephrotoxicity.[10] Although initial steroid resistance is associated with severe disease and adverse outcomes,[21,22] its relationship with CNI toxicity is not reported previously.

Tacrolimus is proposed to have lower potential for nephrotoxicity.[23,24] Although early reports in transplant recipients supported these findings,[25,26] a recent meta-analysis showed that the risk of nephrotoxicity in transplant allografts was similar for CyA and tacrolimus.[27] Although there are no comparative reports, the present retrospective review did not show differences in histological changes and proportion of patients with nephrotoxicity following therapy with either agent.

Although it might be difficult to distinguish histological changes of CNI toxicity from those caused by disease progression, the two features used to define nephrotoxicity in the present study are fairly specific.[8-10] Using criteria similar to those proposed by Kambham *et al.*[13] on serial biopsies, we found that therapy was associated with increased scores for global glomerulosclerosis, tubular atrophy, non-striped interstitial fibrosis, non-nodular arteriolar hyalinosis, and arteriolar smooth muscle vacuolization. It is possible that some of these changes may relate to injury induced by hypertension or persistent proteinuria and/or progression of lesions in FSGS. Furthermore, scores for non-striped interstitial fibrosis and non-nodular arteriolar hyalinosis were higher among biopsies with nephrotoxicity. These observations confirm previous findings in patients with nephrotic syndrome treated with tacrolimus.[7,16] Serial allograft biopsies suggest that arteriolar smooth muscle vacuolization and juxtaglomerular hyperplasia were considered useful indicators of CNI toxicity.[28,29]

In the present patients, there was no demonstrable change in GFR during therapy. A similar lack of correlation between GFR and nephrotoxicity was reported in children with steroid resistant nephrotic syndrome treated with CyA[30] or tacrolimus.[31] Others showed that prolonged

therapy with CyA for up to 10 years in patients with nephrotic syndrome resulted in relatively modest (12%) decline in renal function.[32] A clinical trial on 72 patients with FSGS treated with CyA showed that the median ratio of estimated GFR at 6 months to baseline was 0.73.[33] A recent prospective study at this center in 52 patients treated with tacrolimus for 12 months demonstrated a 10% reduction in GFR.[34]

Findings from the study suggest that one-fourth of the children with steroid resistant nephrotic syndrome show histological evidence of nephrotoxicity following prolonged therapy with CNI. The risk of toxicity was similar in patients receiving CyA and tacrolimus and was increased for patients with initial resistance, persistent hypertension and nephrotic range proteinuria. Our findings emphasize the utility of protocol biopsies and potential for alternative strategies, including the use of mycophenolate mofetil or rituximab, to maintain disease remission.

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