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Original Paper

Second-Line Immunosuppressive Treatment of Childhood Nephrotic Syndrome: A Single-Center Experience

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Key Words

Second-line immunosuppressive treatment · Childhood nephrotic syndrome · Steroid-resistant nephrotic syndrome · Steroid-dependent nephrotic syndrome · Frequent-relapse steroid-sensitive nephrotic syndrome · Tacrolimus · Rituximab

Abstract

Objective: Most cases of idiopathic nephrotic syndrome in childhood are responsive to corticosteroids. However, there is a small group of children that demonstrate steroid resistance (steroid-resistant nephrotic syndrome; SRNS), steroid dependence, or that frequently relapse (frequent-relapse steroid-sensitive nephrotic syndrome; FR-SSNS) which are more clinically difficult to treat. Therefore, second-line immunosuppressants, such as alkylating agents, calcineurin inhibitors, antimetabolites and, more recently, rituximab, have been used with varying success. The objective was to evaluate the response rates of various second-line therapies in the treatment of childhood nephrotic syndrome. **Study Design:** A retrospective chart review of pediatric subjects with idiopathic nephrotic syndrome was conducted at a single tertiary care center (2007–2012). Drug responses were classified as complete response, partial response, and no response. **Results:** Of the 188 charts reviewed, 121 children were classified as SSNS and 67 children as SRNS; 58% were classified as FR-SSNS. Sixty-five subjects were diagnosed with focal segmental glomerulosclerosis via biopsy. Follow-up ranged from 6 months to 21 years. The combined rate of complete and partial response for mycophenolate mofetil (MMF) was 65% (33/51) in SSNS and 67% (6/9) in SRNS. For tacrolimus, the response rate was 96% (22/23) for SSNS and 77% (17/22) for SRNS. Eighty-three percent (5/6) of SSNS subjects treated with rituximab went into complete remission; 60% relapsed after B-cell repletion. Eight refractory subjects were treated with combined MMF/tacrolimus/corticosteroid therapy with a 75% response rate. **Conclusion:** Our experience demonstrates that older medications can be replaced with newer ones such as MMF, tacrolimus, and rituximab with good outcomes and better side effect profiles. The treatment of refractory cases with combination therapy is promising.

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Introduction

Nephrotic syndrome in children presents with the clinical constellation of nephrotic-range proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Idiopathic nephrotic syndrome, namely minimal-change nephrotic syndrome (MCNS), diffuse mesangial proliferation, and focal segmental glomerulosclerosis (FSGS), accounts for 90% of all cases of nephrotic syndrome in children with an incidence in the United States of 2–7 per 100,000 and a prevalence of 16 per 100,000 [1–3]. Treatment of nephrotic syndrome is targeted toward minimizing proteinuria, a known correlate with progression to renal failure and morphological pathology [4–6]. The first-line therapy is universally corticosteroids. Approximately 80% of cases are steroid responsive at presentation, indicating a favorable prognosis for kidney function [1]. For the small fraction of steroid-resistant cases, however, the prognosis is more guarded; 36–50% of children with steroid-resistant nephrotic syndrome (SRNS) progress to end-stage renal disease (ESRD) within 10 years [7, 8]. Children that demonstrate steroid resistance, become steroid dependent (steroid-dependent nephrotic syndrome; SDNS), or frequently relapse (frequent-relapse steroid-sensitive nephrotic syndrome; FR-SSNS) are more clinically difficult to treat.

Although the pathogenesis of SRNS, SDNS, and FR-SSNS is not fully understood, an underlying immunological defect is suspected and therefore serves as the rationale for use of second-line immunosuppressants and immunological interventions in treatment [9]. Such second-line strategies are also utilized to avoid serious side effects of prolonged steroid exposure. Preferences on class and sequencing of immunomodulatory drugs for the treatment of SRNS, SDNS, and FR-SSNS have varied with time and region. Alkylating agents such as cyclophosphamide and chlorambucil, levamisole, and the calcineurin inhibitor cyclosporine have been used for over 20 years [9]. Severe side effects and questionable modes of action, however, have called into favor several new classes of drugs that target various stages of T- and B-cell action. Tacrolimus, a calcineurin inhibitor that inhibits interleukin-2-driven T-cell activation, has shown promising results in various single-centered studies [5, 10–12]. Mycophenolate mofetil (MMF), a T- and B-cell proliferation inhibitor, has been recently introduced for the treatment of SSNS. Although there is limited precedence in treatment of SRNS with MMF, a reduction in the relapse rate of moderately affected patients has been documented in small studies [9, 13]. The monoclonal antibody rituximab is an anti-B-cell treatment that is often used as a ‘rescue medication’ for especially difficult patients. Past studies have shown promising results, although long-term side effects and remission sustainability have been called into question [14, 15].

The aim of this study is to evaluate the response rates of various second-line therapies in the treatment of childhood nephrotic syndrome. Responses to tacrolimus, MMF, rituximab, cyclosporine, and cyclophosphamide were collected for comparison. A rather recent therapy of simultaneous MMF, tacrolimus, and corticosteroid usage based on a pilot study in Japan [16] was also utilized in a small cohort of patients at our center and therefore evaluated in our study. Here, we report our single-center experience with second-line immunosuppressive therapies in pediatric patients with SSNS and SRNS.

Subject and Methods

The study design was that of a retrospective chart review of pediatric subjects <21 years of age with SRNS and SSNS that were evaluated at a single tertiary care center between 2007 and 2012. Subjects with infantile (or congenital) nephrotic syndrome, secondary nephrotic syndrome, glomerulonephritis, or systemic disease were excluded from the study. Subjects were screened for usage of medication therapies. Data were collected for duration of usage

and response rate for each drug in all patients. Drug response was recorded for subjects who completed 2 or more months of therapy. The study was approved by the North Shore-LIJ Health System Institutional Review Board.

Definitions

- SSNS: remission of proteinuria, urine protein:creatinine ratio (UP/Cr) <0.2, with corticosteroids;
- SDNS: subcategory of SSNS; relapse during corticosteroid therapy or within 2 weeks of discontinuing corticosteroids;
- FR-SSNS: >2 relapses in 6 months or ≥4 relapses in 12 months;
- SRNS: failure to induce remission within 8 weeks of corticosteroid treatment;
- complete response: UP/Cr <0.2;
- partial response: proteinuria reduction of >50% and nonnephrotic-range proteinuria, UP/Cr >0.2 and <2, and
- no response: failure to achieve UP/Cr <2 or proteinuria reduction <50%.

Treatment Protocol for Childhood Nephrotic Syndrome

Subjects with new-onset nephrotic syndrome were empirically treated with an initial course of corticosteroids at standard dosing of 60 mg/m² daily for 4–6 weeks followed by a taper of 40 mg/m² every other day for 4–6 weeks. Second-line immunosuppressive therapies were utilized in subjects who were steroid resistant or suffered side effects from prolonged exposure to steroids (i.e. SDNS and FR-SSNS). Subjects showing no response to the initial medication from the second-line group of therapies after 4–6 months or intolerance to a medication were switched to the next medication, generally in the following order: (1) MMF at 600 mg/m² given twice a day; (2) tacrolimus at 0.1 mg/kg divided in 2 doses over 12-hour intervals, with target trough drug levels of 3–5 ng/ml; (3) rituximab at 375 mg/m² per dose until B-cell depletion (1–2 doses), and (4) simultaneous usage of MMF/tacrolimus/prednisone at aforementioned dosing. Subjects with biopsy-proven FSGS were in large part started on tacrolimus and adjunctively treated with angiotensin receptor blockers (ARBs) and/or angiotensin-converting enzyme inhibitors (ACEi). Subjects presenting with nephrotic syndrome before 2007, subjects diagnosed and initially treated at other institutions, and subjects with inadequate compliance may have had varying initial and second-line treatments.

Statistical Analysis

The Student t test and Pearson χ^2 test were used to compare equality of means in demographic data of SRNS and SSNS subjects. The primary outcome variable was the number of subjects who went into complete or partial remission. The secondary outcome variables included maintenance of remission once treated, estimated glomerular filtration rate (eGFR), cholesterol, and blood albumin levels. eGFR was calculated by the Schwartz equation.

Results

Of the 188 subject charts reviewed, 121 children were classified as SSNS and 67 children as SRNS. Fifty-eight percent of SSNS had FR-SSNS. Sixty-five subjects were diagnosed with FSGS via biopsy or genetic testing. Length of follow-up ranged from 6 months to 21 years. The demographic and clinical characteristics of the cohort are shown in table 1. The subject cohort consisted predominately of males (65%). The mean age and age of onset were significantly younger for SSNS than for SRNS. There was a slight predominance of Caucasian and Asian subjects in the SSNS cohort and of African-American subjects in the SRNS cohort. At initial

Table 1. Demographics

	SSNS (n = 121)	SRNS (n = 67)	p values
Current age, years	11.2±5.3	15.6±5.9	<0.001
Age at diagnosis, years	4.8±3.5	8.8±5.6	<0.001
Duration of illness, years	6.4±5.0	6.8±5.1	0.62
Gender			0.55
Male	65% (79/121)	63% (42/67)	
Female	35% (42/121)	37% (25/67)	
Ethnicity			<0.01
Caucasian	34% (41/121)	26% (17/65)	
African-American	16% (19/121)	34% (22/65)	
Hispanic	15% (18/121)	25% (16/65)	
Asian	29% (36/121)	9% (6/65)	
Other	6% (7/121)	6% (4/65)	
BMI at presentation	20.2±11.6	24.7±26.3	0.1
Hypertension at presentation			0.1
Hypertensive	15% (14/92)	30% (17/53)	
Normal	85% (78/92)	70% (36/53)	
Microhematuria at presentation			<0.01
Hematuric	42% (42/100)	23% (13/57)	
Nonhematuric	58% (58/100)	77% (44/57)	
Serum total cholesterol at presentation, mg/dl	395.8±110.7	269.2±168.7	<0.001
UP/Cr ratio at presentation	5.0±4.0	5.2±4.3	0.87
eGFR at presentation, ml/min/1.73 m ²	211.5±102.3	133.3±92.1	<0.001
Biopsy			<0.001
Done	14% (17/121)	84% (56/67)	
Not done	86% (104/121)	16% (11/67)	
Diagnosis (FSGS)	9% (11/121)	81% (54/67)	<0.001

presentation, the SSNS group had significantly greater microscopic hematuria, cholesterol, and eGFR, but a lower rate of hypertension than the SRNS group. Renal pathological evaluation and/or genetic testing showed FSGS in 9% of the SSNS cohort and 80% of the SRNS cohort. The results of treatment are given in table 2.

Response to MMF

Fifty-six SSNS subjects and 10 SRNS subjects were given 1 or more trials of MMF. Adequate response data were available for 51 out of 56 SSNS subjects treated with MMF. Of these 51 study subjects, 32 achieved complete remission (63%), 1 achieved partial remission (2%), and 18 had no response (35%). The combined rate of complete and partial response to MMF was 65% in the SSNS cohort. The mean duration of use was 17.9 months. At last follow-up, of the 32 patients that achieved complete remission, 11 (34%) attained sustained remission off medications, 9 subjects were currently on treatment with MMF, 3 subjects had occasional relapse off MMF, 2 relapsed and were restarted on MMF, and 4 relapsed and were switched to a different medication.

Of 10 SRNS subjects treated with MMF, 1 subject failed to complete an adequate regimen (<2 months of use), 4 achieved complete remission (45%), 2 achieved partial remission (22%), and 3 failed to respond (33%). Two of the 4 subjects that achieved complete remission attained sustained remission off MMF. Two out of 3 subjects who failed to respond progressed to ESRD. The combined rate of complete and partial response to MMF was 67% in the SRNS cohort. The mean duration of use was 18.1 months.

Table 2. Medication history

	SSNS	SRNS
<i>Relapse/remission patterns</i>		
Normal responders	40% (49/121)	0% (0/67)
Frequent relapsers	58% (70/121)	
Relapses/year	5.9±3.0	7.0±1.7
Persistent proteinuria	6% (7/121)	85% (57/67)
<i>MMF</i>		
Usage	46% (56/121)	15% (10/67)
Duration of use, months	17.9±12.4	18.1±13.5
Response		
CR	63% (32/51)	45% (4/9)
PR	2% (1/51)	22% (2/9)
NR	35% (18/51)	33% (3/9)
<i>Tacrolimus</i>		
Usage	19% (23/121)	34% (23/67)
Duration of use, months	31.7±25.6	20.5±19.3
Response		
CR	78% (18/23)	54% (12/22)
PR	18% (4/23)	23% (5/22)
NR	4% (1/23)	23% (5/22)
<i>Rituximab</i>		
Usage	5% (6/121)	6% (4/67)
Response		
CR	83% (5/6)	25% (1/4)
PR	0% (0/6)	0% (0/4)
NR	17% (1/6)	75% (3/4)
<i>Cyclosporine</i>		
Usage	14% (17/121)	19% (13/67)
Duration of use, months	23.9±21.0	29.0±42.0
Response		
CR	57% (8/14)	31% (4/13)
PR	0% (0/14)	23% (3/13)
NR	43% (6/14)	46% (6/13)
<i>Cyclophosphamide</i>		
Usage	9% (11/121)	6% (4/67)
Duration of use, months	2.7±0.8	3.0±9.5
Response		
CR	44% (4/9)	0% (0/3)
PR	0% (0/9)	33% (1/3)
NR	56% (5/9)	67% (2/3)
<i>ACEi/ARB</i>		
Usage	20% (24/121)	65% (44/67)

CR = Complete remission; PR = partial remission; NR = no remission.

Response to Tacrolimus

Twenty-three SSNS subjects and 23 SRNS subjects received 1 or more trials of tacrolimus. Thirteen subjects in whom MMF failed were switched to tacrolimus; of these, 8 responded to tacrolimus. Eighteen out of 23 SSNS subjects achieved complete remission on tacrolimus (78%), 4 achieved partial remission (18%), and 1 subject failed to respond (4%). The combined rate of complete and partial response to tacrolimus was 96% in the SSNS cohort.

The mean duration of use was 31.7 months. At last follow-up, of those that achieved complete remission, 6 were currently on treatment, 8 subjects relapsed and were switched to a different medication, and 1 relapsed and was restarted on tacrolimus.

Twelve out of 22 SRNS subjects who received tacrolimus therapy achieved complete remission (54%), 5 achieved partial remission (23%), and 5 failed to respond (23%). Two out of 5 SRNS subjects who failed to respond to tacrolimus progressed to ESRD. The combined rate of complete and partial response to tacrolimus was 77% in the SRNS cohort. The mean duration of use was 20.5 months. At last follow-up, those that attained complete remission are still on the medication.

Response to Rituximab

Six SSNS subjects and 4 SRNS subjects received 1–2 cycles of rituximab (1–2 doses per cycle). Five out of 6 (83%) SSNS subjects treated with rituximab went into complete remission shortly after receiving the drug. Three of the 5 (60%) who responded relapsed after B-cell repletion (average 7.2 months after treatment) and were given another cycle of rituximab. The length of follow-up since the first cycle was a median of 25.5 months (range 7–41). Three out of 4 (75%) SRNS subjects treated with rituximab failed to respond to the drug. One subject progressed to ESRD after receiving 1 cycle of the drug, while in 2 subjects rituximab therapy failed, yet they eventually achieved partial and complete remission on simultaneous MMF/tacrolimus/prednisone therapy. There were mild allergic reactions in 2 subjects during rituximab infusion.

Response to Cyclosporine

Seventeen SSNS and 13 SRNS patients were treated with cyclosporine. Among 17 treated SSNS patients, response data were available for 14 subjects. Eight patients achieved complete remission (57.14%), no patients achieved incomplete remission, and 6 patients failed to respond (42.86%). The mean duration of use was 23.9 months.

Response data were available for all 13 SRNS patients treated with cyclosporine. Four patients achieved complete remission (30.77%), 3 patients achieved partial remission (23.08%), and 6 patients failed to respond (46.15%). The mean duration of use was 29 months.

Response to Cyclophosphamide

Eleven SSNS patients and 4 SRNS patients were treated with cyclophosphamide.

Adequate data were available for 9 SSNS subjects. Four out of 9 test subjects achieved complete remission (44.44%), no patients achieved partial remission (0%), and 5 patients failed to respond (55.56%). The mean duration of use was 2.7 months.

Of the 4 SRNS patients who received cyclophosphamide therapy, response data were available for 3 subjects. No patients in this cohort achieved complete remission (0%), 1 patient achieved partial remission (33.33%), and 2 patients failed to respond (66.67%). The mean duration of use was 3 months.

Response to Simultaneous MMF/Tacrolimus/Prednisone Therapy

The clinical characteristics of 8 subjects who received simultaneous MMF/tacrolimus/prednisone therapy are documented in table 3. There were 6 males and 2 females, with a median age of onset at 3.0 years (range 1.5–10.4). Two subjects were diagnosed with FSGS, while the remaining 6 subjects were diagnosed with biopsy-proven MCNS. Of the 6 subjects with MCNS, 4 subjects had FR-SSNS (cases 4, 5, 7, and 8), whereas 2 subjects suffered from persistent nephrotic-range proteinuria (cases 1 and 3). All subjects had received immunosuppressive therapy prior to simultaneous therapy. The median treatment duration was 9.5 months (range 4–39); the median follow-up period was 11 months (range 6–75).

Table 3. Simultaneous MMF/tacrolimus/corticosteroid therapy

Case No.	Gender	Race	Age at onset, years	Age at start of combination therapy, years	Renal pathology	Previous immunosuppressants	Duration of combination therapy, months	Response to combination therapy	Response time, months	Lowest known UP/Cr	Final eGFR, ml/min/1.73 m ²	Final serum albumin, mg/dl	Follow-up, months
<i>SRNS</i>													
1	male	South Asian	2	4	MCNS	pred, tac, rituximab	11	PR	6	1.23	140.3	3.7	11
2	female	South Asian	1.5	6	MCNS	pred, levamisole, cyclo, MMF	15	CR	<1	0.08	153.7	4	15
3	male	South Asian	3.2	5	MCNS	pred, tac, rituximab	11	CR	6	0.14	206.9	3.8	11
<i>SDNS</i>													
4	male	African-American	10.4	19	MCNS	pred, cyclo, MMF, tac	4	NR		0.07	124.2	3.3	10
5	male	Caucasian	8.6	9	MCNS	pred, MMF	6	CR	<1	0.08	135.7	4.5	10
6	male	Asian	8	11	FSGS	pred, MMF	8	NR		7.22	48.5	1.5	75
<i>SSNS</i>													
7	male	Asian	2	17	MCNS	pred, cyclo, MMF	39	CR	6	0.05	156.3	4.2	45
8	female	Caucasian	2.8	7	FSGS	pred, cyclo, tac	6	CR	1	0.19	103.3	4	6

pred = Prednisone; tac = tacrolimus; cyclo = cyclosporine; PR = partial remission; CR = complete remission; NR = no remission.

Of the 8 children treated with simultaneous therapy, 5 (63%) achieved complete remission, consisting of 2 (67%) SRNS subjects and 3 (60%) SSNS/SDNS subjects. The combined rate of complete and partial response in this 8-subject cohort was 75%. Cases 2, 5, and 7 stopped relapsing altogether within 6 months of starting therapy. Cases 2 and 5 were eventually weaned off all medications. Case 7 remained on simultaneous therapy and in complete remission until drug noncompliance led to 3 relapses in 2 months. The subject was subsequently placed on prednisone in addition to correct simultaneous MMF/tacrolimus/prednisone dosing and promptly achieved complete remission once again. Case 3, who had persistent nephrotic-range proteinuria, went from an initial UP/Cr of 3.64 to a lowest UP/Cr of 0.14. One of 2 FSGS subjects (case 8) achieved complete remission within 1 month of starting therapy, with a reduction in UP/Cr from 2.8 to 0.08. Both subjects with persistent proteinuria achieved a complete and nontransient remission on simultaneous therapy. Eighty percent of subjects who went into complete remission showed a complete, nontransient response. Those with complete response were able to wean off prednisone. Although classified as partial remission, case 1 had a 94% reduction in proteinuria and significant improvement in serum albumin and edema. The subject had been on a steady downward trend in proteinuria over an 11-month follow-up period and was thus continuing simultaneous therapy at the last follow-up visit.

Discussion

Treatment of SRNS, SDNS, and FR-SSNS in children can often prove to be challenging. There is a paucity of large-scale randomized controlled trials that provide strong evidence to guide therapy. Recently, KDIGO (Kidney Disease: Improving Global Outcomes) released a clinical practice guideline on the treatment of SSNS and SRNS [17]. For FR-SSNS, the guidelines 'recommend' the use of the alkylating agents cyclophosphamide and chlorambucil as corticosteroid-sparing agents with moderate quality of evidence (1B) and 'suggest' the use of

alkylating agents in SDNS with low quality of evidence (2C). Although these guidelines are supported by evidence showing a relative risk reduction of 56% for cyclophosphamide, long-term remission rates have proven poor in more recent literature [17]. Two studies documented that only 30–35% of patients with minimal-change disease reached long-term remission after cyclophosphamide treatment [16]. Because of potential for gonadal, hematologic, and other toxicities of alkylating agents and availability of newer therapeutic agents, we have not recently used cyclophosphamide at our center. The patients reported in this study had predominantly taken cyclophosphamide 5 or more years prior to our retrospective chart review and often at outside institutions, making it difficult to gauge initial response. Nonetheless, our experience shows that initial response to cyclophosphamide is poor. All patients with a history of cyclophosphamide usage eventually relapsed and required alternative therapies.

Cyclosporine (CsA) is yet another drug with great precedence in the field of pediatric nephrology, supported as well by the KDIGO guidelines. Studies old and new have shown that CsA may serve as a primary choice for second-line treatment of childhood nephrotic syndrome [16, 18]. Past studies have shown response rates as high as 82% in children with MCNS and 86% in children with FSGS [19]. Our results for response to cyclosporine, however, were much lower. Although our data and past literature show moderate to excellent response rates to CyA, it is associated with both dangerous and unattractive side effects such as nephrotoxicity, hypertension, hypertrichosis, and gum hyperplasia. As a result, tacrolimus has been the calcineurin inhibitor of choice at our institution.

Tacrolimus has recently been investigated as an alternative to cyclosporine for its milder side effects and efficacy, although it has been proven neither superior nor inferior [20]. Initial studies on tacrolimus documented outcomes similar to those seen in our study for the SRNS cohort, although no studies have been published on its long-term side effects. Little literature is available on the effects of tacrolimus on steroid-sensitive patients. However, our study suggests good outcomes; we discovered a 96% combined complete and partial response in patients with SSNS. Despite our promising findings on the success of treating SSNS patients with tacrolimus, nephrotoxicity remains a significant concern. Hence, MMF is our preferred initial therapy for patients starting on second-line immunosuppressive treatment.

MMF is a drug with a milder side effect profile that works by inhibiting purine synthesis via disruption of inosine monophosphate dehydrogenase [21]. Our results are consistent with past literature [9, 13]; MMF is effective in treating SSNS but seems to be less effective in SRNS and severely affected patients. The combined rate of complete and partial remission, however, in SRNS patients is modestly greater than that of SSNS patients. Our findings suggest that MMF is an adequately potent agent in targeting proteinuria in both steroid-sensitive and steroid-resistant patients; however, relapse rates are high. It is important to note, however, that extensive studies on the long-term side effects and dependency have not as of yet been investigated.

Rituximab, a monoclonal antibody that targets B-cells, is a relatively new treatment that is often used for refractory cases of nephrotic syndrome [9]. Our findings indicate that rituximab is extremely effective in patients with refractory SSNS, regardless of renal pathology. Of the 6 SSNS patients treated with rituximab, 5 patients showed a complete response. This is similar to the literature, with reports of two-thirds of patients treated maintaining long-term remission [22, 23]. However, our patients had a high relapse rate necessitating repeat rituximab infusions. Rituximab is promising in the treatment of refractory cases of nephrotic syndrome; however, the long-term effects of this treatment are unknown.

In this study, we present the results of a combination therapy which entails the simultaneous administration of MMF, tacrolimus, and corticosteroids. Our results indicate that simultaneous therapy was successful in treating extremely difficult patients. There have been pilot

studies for the use of combined MMF/tacrolimus/steroid therapy in treating both adult and pediatric nephrotic syndromes [16, 24]. The pilot study in pediatrics similarly found a combination therapy of tacrolimus, MMF, and steroids in children had a combined complete and partial response rate of 86% [16]. Aizawa-Yashiro et al. [16] focused on a cohort of CyA-resistant or -intolerant patients on which to test the effects of combination therapy. Although our results are based on a smaller cohort, the patients in our cohort were resistant to a wider variety of second-line immunosuppressives including tacrolimus and MMF alone. This suggests a fundamental difference in the mechanism of action in simultaneous therapy than each drug's singular action.

Although the study is comprehensive, it has limitations. Firstly, the study cohorts lacked homogeneity in demographics, patient history, and follow-up. As a retrospective chart review, study subjects had no mandated follow-up period and no histological reevaluation. Many were therefore lost to follow-up. Among those patients reviewed retrospectively, 4 FSGS patients received drugs (specifically cyclosporine and MMF) as part of an unrelated protocol (FSGS Clinical Trial).

Despite such limitations, we believe this single-center retrospective chart review offers a comprehensive profile for second-line drug usage in the treatment of childhood idiopathic nephrotic syndrome. Many of our findings prompt further investigation into novel therapies as well as the reevaluation of current treatment regimens. We regard the treatment of difficult cases with simultaneous therapy and the replacement of cyclosporine/cyclophosphamide with newer drugs such as MMF, tacrolimus, and rituximab as promising.

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