

Evaluation and management of steroid-unresponsive nephrotic syndrome

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Purpose of review

Idiopathic nephrotic syndrome in children is commonly associated with minimal change disease and response to steroid therapy. Steroid-unresponsive nephrotic syndrome is often characterized by persistent proteinuria and progression to chronic kidney disease. Focal segmental glomerulosclerosis is the leading cause of steroid-unresponsive nephrotic syndrome in childhood. There is no uniformed consensus as to the treatment of steroid-unresponsive nephrotic syndrome. Advances in the pathogenesis, genetics and biomarkers or surrogate markers may be useful for the diagnosis and identification of patients with steroid-unresponsive nephrotic syndrome, severity of disease, progression and response to therapy.

Recent findings

This review is intended to describe some of the recent changes in the epidemiology of steroid-unresponsive nephrotic syndrome, in particular focal segmental glomerulosclerosis, its pathogenesis and alternative therapies.

Summary

Recent studies in both children and adults have shown an increase in the incidence of focal segmental sclerosis as a cause of steroid-unresponsive nephrotic syndrome. Advances in the pathogenesis and noninvasive methods of diagnosis may allow for the identification of steroid-responsive patients.

Keywords

focal segmental glomerulosclerosis, nephrotic syndrome, steroid-resistant nephrotic syndrome, steroid-sensitive nephrotic syndrome

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Introduction

The treatment of steroid-resistant nephrotic syndrome (SRNS) in childhood remains controversial despite the long-standing recognition that idiopathic nephrotic syndrome (INS) is a clinicopathologic entity characterized by the presence of proteinuria, edema, hypoalbuminemia and hypercholesterolemia. The International Study of Kidney Diseases in Children (ISKDC) evaluated a large number of patients with INS and described the pathologic lesions found in these patients prior to institution of therapy. Minimal change disease (MCD) accounted for 60–85% of INS followed by idiopathic focal segmental glomerulosclerosis (FSGS), mesangial proliferative, membranous proliferative glomerulonephritis (MPGN), and membranous nephropathy. Approximately 95% of MCD patients responded to a 4-week course of daily oral prednisone at 60 mg/m²/day followed by 40 mg/m²/day on alternate days for an additional four weeks, defining steroid-sensitive nephrotic syndrome (SSNS) [1,2]. Although the incidence of INS has remained stable over the past three decades, recent studies in both children and adults have shown an increase in the incidence of

steroid-resistant FSGS among patients with INS, which may actually be underreported because renal biopsy is only performed in patients who are steroid-unresponsive or resistant [3,4^{*},5^{*},6,7^{**},8^{*}]. Although glucocorticoids are an accepted first-line treatment, only 15–25% of patients with idiopathic FSGS will achieve complete remission [9^{*}]. FSGS is the most common glomerular cause of chronic kidney disease leading to end-stage renal disease (ESRD), with a high recurrence rate in the transplanted kidney of 30–40% [10^{*}].

Classification of steroid-resistant nephrotic syndrome secondary to focal segmental glomerulosclerosis

Primary or idiopathic FSGS has no antecedent cause and accounts for the majority of pediatric patients with SRNS. Secondary FSGS may be due to HIV, morbid obesity and a variety of autoimmune-mediated glomerulonephritides such as systemic lupus erythematosus. Evidence supporting an immune-mediated cause in the pathogenesis of INS stems from experimental and observational clinical data that alterations in the permselectivity of the

glomerular basement membrane may be responsible for the albuminuria in FSGS and localizes the glomerular podocyte as the site of injury [11^{••}]. Podocyte loss and a variety of cytokines and vasoactive factors play a role in the progression of renal injury and offer opportunities for therapeutic interventions [11^{••}].

FSGS is not one disease but a clinically and genetically heterogeneous entity characterized by a glomerular pattern of injury, with five distinct histological patterns: perihilar (lesions predominate in the vascular pole); tip lesions (located in the urinary pole); cellular variant (endocapillary hypercellularity); the collapsing variant (collapse of the glomerular tuft associated with podocyte hypertrophy and hyperplasia); and FSGS with a lesion not otherwise specified (NOS) [12,13]. The collapsing type of FSGS is associated with a rapid progression to ESRD [14[•],15[•]]. A recent retrospective study [16[•]] compared the clinical outcome of 39 pediatric patients with idiopathic FSGS; 11 had collapsing FSGS and the remaining had noncollapsing FSGS. Most patients were African-American and there was equal sex distribution for those with collapsing FSGS. At the end of 31.5 months, 73% of those with collapsing FSGS had chronic kidney failure versus 29% with noncollapsing FSGS. Surprisingly, only one patient in the former group reached ESRD, which may have reflected therapy with cyclosporin A (CsA), mycophenolate mofetil (MMF) and angiotensin converting enzyme inhibitor (ACEI). Silverstein *et al.* [17[•]] conducted a retrospective analysis of 41 patients with idiopathic FSGS to assess the impact of the FSGS variant on clinical features and renal survival. Although the time of observation was only 4 years, they found that the most common variant was NOS with the best overall prognosis, whereas those with the collapsing form had higher blood pressures and lower renal function. Interestingly, and in contrast to other studies, there was no short-term difference in renal survival between African-American and white patients with idiopathic FSGS.

Evaluation

SSNS and SRNS have similar clinical presentations and there are no specific laboratory parameters to distinguish these two clinical entities. The most important predictor of steroid responsiveness is the remission of the proteinuria, as defined by a negative to trace urine dipstick for three consecutive days or a spot urinary protein-to-creatinine ratio (Up/c) under 0.2. In a cohort study of 60 children and adolescents (58% African-American) with biopsy-proven FSGS, from the Glomerular Disease Collaborative Network (GDCN), Gipson *et al.* [18[•]] found that complete remission was associated with a 90% decreased risk of ESRD in a multivariate analysis performed over the 48 months of the study. The univariate analysis showed

that renal survival was much improved in patients with complete or partial remission compared with no remission. For those with SRNS, a biopsy of the renal cortex is necessary to determine the pattern of glomerular injury. Identification of noninvasive biomarkers that differentiate SSNS from SRNS would be most beneficial to steroid-resistant patients, preventing their exposure to high-dose steroids. With the use of urine proteomics, Khurana *et al.* [19[•]] identified β_2 microglobulin as a biomarker associated with SRNS in patients with biopsy-proven FSGS. Woroniecki *et al.* [20[•]] identified the cytokine TGF- β_1 as a marker associated with SRNS due to FSGS. In both studies, these biomarkers were not predictive of steroid responsiveness. In the last decade, genetic linkage studies coupled with positional cloning have identified new genes and proteins, especially the structural podocyte-associated proteins, nephrin, podocin, α -actinin-4, and CD2AP, that when mutated are associated with SRNS, including familial forms of FSGS [21[•]–23[•],24^{••}]. In particular, Schwab *et al.* [25] were able to obtain a gene expression profile of kidney specimens from patients with FSGS. At this point, however, it is not clear if mutations in or expression of these genes will predict response to therapy or long-term kidney survival [24^{••},26[•]], but the recommendation to screen for the known mutations is warranted especially in patients who are steroid-resistant.

Treatment of steroid-resistant nephrotic syndrome

The 'nonspecific' interventions in the management of SRNS with persistent proteinuria include a supportive regimen of interruption of the renin-angiotensin system with ACEI or angiotensin type II receptor blocker (ARB), even in the absence of elevated blood pressure, diuretic therapy as needed to control edema along with a salt-restricted diet, and statins for hyperlipidemia unresponsive to dietary management with low cholesterol/saturated fat [27^{••}]. Indeed, there is suggestive evidence that HMG-CoA reductase inhibitors may decrease proteinuria and limit progression of kidney injury [28^{••}]. Some of the mechanisms responsible for the renoprotective effects of ACEIs or ARBs to diminish proteinuria and slow progression of renal disease involve a decrease in the glomerular capillary hydrostatic pressure and an inhibition of angiotensin II-associated cytokine release and inflammation [29^{••}]. Studies in children are few but also support the antiproteinuric action of ACEI in children with varying causes for chronic kidney disease [30] and with SRNS [31]. Therapies with plasmapheresis, antifibrotics and antioxidants lack randomized controlled investigations.

Experience with sequential therapy was first reported by Tune *et al.* [32], who demonstrated that administration of high doses of methylprednisolone (30 mg/kg) to children with SRNS resulted in improvement in the proteinuria.

Nammalwar *et al.* [33[•]] found that intravenous methylprednisolone and cyclophosphamide and oral prednisone in patients with SRNS equally comprising MCD, mesangial proliferative glomerulonephritis and FSGS resulted in remission in 82, 67 and 17%, respectively, at 3 years. More recently, Peña *et al.* [34[•]] reported the efficacy of a similar sequential treatment with methylprednisolone over 18 months in 30 SRNS children, 24 of whom also received cyclophosphamide. This therapy resulted in a total and partial response in 73.3 and 10%, respectively, with 21 of 22 remaining in remission after 6 years of follow-up while 20% developed steroid dependence. Interestingly, Chang *et al.* [35[•]] found that low-dose methylprednisolone (10 mg/kg) for 8 weeks in eight children with SRNS, along with an alkylating agent or CsA, resulted in a 75% remission. Finally, experience at one center with the use of methylprednisolone pulses plus CsA in children with SRNS resulted in a better outcome than in patients treated with oral prednisone and CsA [36[•]].

Cyclosporin

The calcineurin inhibitor CsA from the fungus *Tolypocladium inflatum* inhibits T-helper cell IL-2 production and causes renal arteriolar vasoconstriction and permselectivity changes in the glomerular basement membrane [37]. The first demonstration that CsA was efficacious in inducing a remission in proteinuria in SRNS children and adults came from Ponticelli *et al.* [38]; although the total number of patients with FSGS was small, 6 months of CsA treatment resulted in a response of 57% versus 16% in the control group. Subsequently, Lieberman *et al.* [39] found that, in 31 children with SRNS secondary to FSGS randomized to either CsA versus placebo for 6 months, 60% of the treatment group had either complete or partial remission. Unfortunately, despite a significant response rate, when CsA was discontinued by 1 year all patients relapsed. Cattran *et al.* [40] also demonstrated a favorable response rate to CsA and low-dose prednisone administration for 26 weeks and a stabilization of estimated kidney function in 49 SRNS adult patients. Partial or complete remission of proteinuria was seen in 70% of the treatment group versus 4% in the placebo group but 40 and 60% of the responders had relapsed by 52 and 78 weeks, respectively. Nevertheless, the creatinine clearance was higher in the treatment group. A report by El-Husseini *et al.* [41] found low-dose CsA to be effective in inducing a remission in 70% of children with SRNS and FSGS. CsA monotherapy induced remissions in 86% of steroid-dependent [30] and 42% of SRNS [11^{••}] patients, although patients with onset of disease below 18 months of age became CsA-dependent [42[•]]. Bagga [43[•]] emphasized the importance of adequately powered and designed randomized controlled trials to assess the utility of these different treatment regimens in SRNS children.

In order to clarify some of the controversies in the field, a recent international workshop made recommendations and developed specific algorithms regarding the use of CsA in most histologic variants of the INS in both children and adults [44^{••}] and emphasized careful monitoring of renal function, minimizing the maintenance dose and utilizing repeat renal biopsy in patients on long-term therapy. Ongoing investigations include the measurement of either trough CsA blood levels or at 2 h after dose, and the benefit of once-daily and preprandial administration of CsA.

Two recent reviews with meta-analyses of the literature for evidence-based studies on the treatment of idiopathic SRNS in children reached similar conclusions that available evidence suggests a beneficial effect of CsA on remission rates compared with placebo or no treatment, irrespective of renal pathology and of cyclophosphamide, on time to remission [45^{••}]. Hodson *et al.* [46^{••}] performed a Cochrane review of 11 small, randomized controlled trials involving 312 children for interventions for idiopathic SRNS. Again, CsA was found to increase the complete remission rate and ACEI with foscipril and prednisone significantly reduced proteinuria after 12 weeks of treatment compared with prednisone alone in 45 children. No randomized controlled trials, however, have compared combination regimens of high-dose steroids, alkylating agents or CsA with single agents, placebo, or no treatment. A well designed adequately powered randomized controlled trial comparing CsA with other treatment in children with SRNS without genetic mutations is required.

Mycophenolate mofetil

MMF is a purine synthetase inhibitor that inhibits synthesis of T and B-cell lymphocytes. Its utility as an immunomodulatory agent used in organ transplantation is well known but its application to treatment of glomerular diseases is new. MMF with concurrent steroids in 18 FSGS patients who were either SRNS or steroid/CsA-dependent [47] resulted in 48% lowering in the urine protein-to-creatinine ratio with a complete and partial remission in two and six patients, respectively. Another study using MMF in 18 SRNS patients, 75% of whom had failed therapy with a calcineurin inhibitor or a cytotoxic agent, found that 6 months of treatment resulted in a reduction in proteinuria in 10 patients and no change in serum creatinine or reports of toxicities [48]. Further evidence supporting a beneficial effect on proteinuria in SRNS FSGS patients was found by Montane *et al.* [49] in nine patients receiving MMF and pulse steroids. Overall, MMF is a useful immunosuppressant with minimal side-effects and effectiveness in maintaining remission in steroid-dependent nephrotic syndrome patients [50[•]] and newer reports indicate it has CsA or steroid-sparing advantages [51[•]].

Sirolimus

Sirolimus is an immunomodulatory agent that blocks cytokine-dependent T-cell proliferation. Tumlin *et al.* [52^{*}] reported on 21 SRNS FSGS patients given a 26-week course of sirolimus and demonstrated a complete and partial remission in 19 and 38%, respectively, with maintenance of the glomerular filtration rate versus controls. The potential for acute renal injury with this agent is suggested by several reports [53].

Tacrolimus

The macrolide antibiotic tacrolimus inhibits CD4 helper cells and is believed to be more potent in suppressing cytokines than cyclosporine. A retrospective study by Loeffler [54] in 16 children with SRNS, some of whom failed treatment with cyclosporine, found that tacrolimus induced a complete and partial remission in 81 and 13%, respectively. Subsequently, a prospective study of 20 children with SRNS secondary to FSGS found tacrolimus and low-dose prednisone for 12 months to be effective in inducing remission or partial remission in 40 and 45%, respectively, although upon cessation most patients relapsed but had no evidence of calcineurin nephrotoxicity on repeat renal biopsy [55^{*}].

An orally available antifibrotic agent, pirfenidone, had no effect on proteinuria during 13 months of treatment in 18 patients with FSGS but slowed the progression of renal injury [56^{*}]. Recent reports describing the successful use of the anti-CD20 monoclonal antibody rituximab in the treatment of recurrent FSGS and SRNS in children suggest a potential role for this agent in the management of difficult cases of INS [57^{*},58^{*}].

Design and implementation of the National Institutes of Health focal segmental glomerulosclerosis treatment trial

In response to the need for rigorously tested treatment modalities for idiopathic SRNS secondary to FSGS, the US National Institutes of Health sponsored the FSGS Clinical Trial (FSGS-CT; <http://fsgstrial.org>) [59^{**}]. It is a phase III randomized trial of children and young adults aged 2–40 years being conducted at over 100 sites in North America. Eligibility criteria include biopsy-confirmed primary FSGS, corticosteroid resistance as evidenced by a Up/c over 1.0 during a minimum 4 weeks prednisone therapy with a cumulative minimal dose of 56 mg/kg prednisone or equivalent, persistent proteinuria (Up/c >1.0), and an estimated glomerular filtration rate (GFR) of 40 ml/min/1.73 m² or higher. Exclusion criteria include secondary FSGS, prior therapy with CsA, tacrolimus, MMF, sirolimus, or azathioprine, and obesity.

In evaluating the therapeutic interventions chosen for the FSGS-CT, consideration was given to the fact that there was no evidence-based medicine to suggest that any specific therapeutic intervention for the treatment of steroid-resistant FSGS would provide a significant reduction in proteinuria or preservation of renal function in a substantially large proportion of participants. The following four factors, however, were taken into consideration in the ultimate design of the clinical trial: an established role for CsA in the treatment of FSGS; the potential but unproven benefit of intermittent high-dose corticosteroid therapy in combination with another immunosuppressive agent; the efficacy of either therapeutic intervention to induce sustained reduction in proteinuria after withdrawal of a therapeutic agent; and the side-effects and consequence of any long-term therapeutic intervention, if withdrawal of medication is unsuccessful.

The primary outcome is attainment of partial or complete remission and the main secondary outcome is relapse after withdrawal of immunosuppressive agents followed by treatment failures, change in estimated GFR, side-effects, quality of life and receipt of biological materials. Patients are randomly assigned to one of two active treatment arms: CsA or pulse MMF plus dexamethasone. The target period for maintaining these medications is 12 months. Both study groups are also treated with either lisinopril or losartan for 18 months and low-dose alternate-day steroids for 6 months. The decision to include alternate-day corticosteroid therapy and inhibition of the renin-angiotensin system as background therapy for both therapeutic arms of this clinical trial reflected current standards of practice. Most therapeutic interventions of participants with steroid-resistant FSGS included these two elements irrespective of the primary therapeutic intervention. The ultimate effectiveness of therapeutic intervention could be appreciated best if it were possible to sustain an anti-proteinuric effect when the medication was withdrawn.

The primary outcome is based on achievement of remission of proteinuria: complete remission Up/c <0.2; partial remission Up/c <50% of baseline value and <2; or no remission. Patients who do not achieve a complete or partial remission at 6 months are defined as treatment failures for the primary outcome, and exit the study. Thus, patients entering the study commit to only 6 months of therapy unless a remission is achieved. The primary outcome for the remaining patients will be assessed at month 12. The main secondary outcome is the persistence of remission after withdrawal of the CsA or MMF/dexamethasone during study months 12–18. The analysis will be carried out by intent-to-treat with patients retained in their randomized groups regardless of whether they have maintained and adhered to their randomly assigned treatment regimen.

Conclusion

The incidence of SRNS secondary to FSGS is increasing and urges a new approach to its causes and management using the scientific analyses of randomized controlled trials. The FSGS-CT is the largest controlled trial of FSGS in North America and will establish a standard for therapy for corticosteroid-resistant primary FSGS. Additional benefits of the trial are the establishment of an infrastructure for the study of FSGS, creation of a national repository of biospecimens for investigation of the pathogenesis of FSGS and the role of histologic sub-classification of FSGS and the response to therapies and the evaluation of the efficacy of withdrawing immunosuppressive drugs while maintaining ACEIs/ARBs. This opportunity will serve as a template for subsequent design and implementation of investigations into the causes, prevention and treatment of a variety of progressive glomerular disorders.

Acknowledgements

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 225).

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