

Invited Article

Steroid-Resistant Focal Segmental Glomerulosclerosis: Critiques on Combined Therapeutic Regimens

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Abstract

Objectives: We aim to review the therapeutic options in ameliorating the progression of steroid resistant-focal segmental glomerulosclerosis (SR-FSGS). We shall comment on the clinical implications of candidate genes in familial cases of FSGS. **Methods:** Selected key references concerning SR-FSGS were analysed, together with a PubMed search of the literature from 1998 to 2009 and a search on current clinical trials registered with ClinicalTrials.gov. **Findings:** Treatment options consist of one or more of the following medications: vitamin E, prednisone, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker. In the resistant cases, methylprednisolone, cyclophosphamide, cyclosporine, calcineurin inhibitors, rituximab, galactose, and mycophenolate mofetil have been used. In this review, the current clinical trials in SR-FSGS are critiqued. The new findings on the genetics of familial forms of FSGS are reviewed. **Conclusions:** The available modalities of treatment are only moderately effective. Research into the genetics of familial FSGS may finally provide insight into the pathogenesis of injury to the podocytes, central to the development of FSGS and may point to novel therapy to improve the long-term outcome of SR-FSGS.

Key words

Cyclosporine; Focal segmental glomerulosclerosis; Galactose

Introduction

Focal segmental glomerulosclerosis (FSGS) is the common pathway of various types of renal injury.¹ We shall

highlight the clinical characteristics and history of the changing therapeutic approaches, including the experimental evidence of vitamin E in reversing established FSGS. We shall comment on the search for prognostic indicators² and review the impact and limitations of recent clinical trials to modulate the progression of steroid resistant-FSGS (SR-FSGS).³ Finally, we shall recount the current understanding of genetics in familial FSGS.

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Methods

Key references concerning FSGS were evaluated, in concert with a PubMed literature search from 1998 to 2009 and a <ClinicalTrials.gov> search. The most current and relevant information from the literature pertaining to FSGS, and in particular to SR-FSGS, was reviewed.

Findings

Nephrotic syndrome occurs at an annual rate of 2 to 7 new cases per 100,000 children (under 18 years of age).⁴ According to the landmark International Study of Kidney Disease in Children,⁵ for nephrotic syndrome, minimal change disease accounts for 77% and FSGS accounts for 8% of the cases.

The vulnerability of juxta-medullary glomeruli to sclerotic changes was first described in 1957 and the use of the word "focal" to describe this location was advocated by Habib⁶ since 1974.

FSGS Histology and Predictors of Progression

The realisation that FSGS is not a single disease but a histological pattern of kidney injury is gaining wide acceptance.^{3,4} However, the field is confused by different descriptors for the same histological lesions. To clarify this issue, the Kidney and Urology Foundation of America appointed a working group in 2004,⁷ to come up with recommendations. The Group concluded that the histological lesions of FSGS be classified into the following variants: 1) collapsing; 2) tip; 3) cellular; 4) perihilar; and 5) "not otherwise specified" or classic FSGS. The key priority is for investigators to describe FSGS by this classification,⁷ which will go a long way for clarity in future research efforts. As it now stands, the clinical implications of this histologic classification are that the collapsing variant has the worst prognosis, being both resistant to all therapeutic efforts and having a more rapid progression to end-stage kidney failure.^{3,7} In the collapsing form of FSGS, the disease is marked by severe hypertension, more massive proteinuria, poorer response to corticosteroids, and a faster rate of progression to end-stage renal disease (ESRD).⁷ Currently, the other variants have about the same inconsistent responses.

Less reliable predictors of progression are race, with black adult patients fairly likely to progress more rapidly to ESRD. Prognosis is less favorable in the males of all ethnicities.

Baseline data of total cholesterol, urinary protein/creatinine ratio, and steadily reduced calculated glomerular filtration rate (cGFR) are not strong predictors of progression to ESRD.² Severely overweight patients with body mass index (BMI) in the range of 46±11 are associated with FSGS and kidney failure. However, in a recent analysis of data collected over 25 years, BMI in the range of 24±9, is not a risk factor of kidney disease progression.²

Unsuccessful control of systolic hypertension has been

considered to be a definite risk factor for kidney injury and progression to kidney failure. The finding of higher diastolic blood pressure at baseline in the kidney failure group is an under-recognised risk factor.²

Primary and Secondary FSGS

It is beginning to be widely accepted that the key defect in primary FSGS lies in the mutation of podocyte protein.³ The clinical presentation includes nephrosis, hypertension, haematuria, and elevated serum creatinine. It is recognised that relapses of FSGS occurs in 30% of kidney transplant allograft. Finally, secondary FSGS occurs from a host of conditions (Table 1), which need to be excluded by history, physical examination and diagnostic workup.

Evolution of Therapeutic Regimens

The approach to treatment of FSGS can be arbitrary divided into phases by decades (Table 2) – more for convenience to delineate a time line in the evolution of therapeutic regimens – as we learn from what was not working and some approaches which seem to be hopeful.

In the first phase, the decade from 1970 to 1980 (Table 2), Habib⁶ recommended that no steroid treatment be used, because the disease is unresponsive to steroids. Also, the side effects of long-term, repeated use of high dose steroids,

Table 1 Secondary focal segmental glomerulosclerosis

Presenting with nephrotic syndrome

- Diabetic nephropathy
- Morbid obesity
- HIV nephropathy
- Sickle cell disease
- Heroin-associated nephropathy
- Denys-Drash syndrome
- Frasier syndrome
- Pierson syndrome
- Congenital nephrotic syndrome of the Finnish type

Unusual to present with nephrotic syndrome

- Reflux nephropathy
- Renal dysplasia
- Renovascular disease
- Single kidney (acquired, or congenital)
- Alport syndrome (familial hereditary nephritis)
- Barter syndrome
- Dent disease-1 (X-linked recessive nephrolithiasis)
- Lowe syndrome (OCRL1 mutation, Dent disease-2)
- Renal tubular acidosis

Table 2 Evolving combined therapeutic regimens to SR-FSGS in four decades

Phase 1: 1970-1980	Habib ⁶ recommended no steroid therapy because it was ineffective and daily steroids had marked side-effects.
Phase 2: 1980-1990	Low dose, alternative day prednisone (1.5 mg per kg every other day or 40 mg/meter ² every other day) ± levamisole (2.5 mg/kg every other day) ± cyclophosphamide (2 mg/kg/day).
Phase 3: 1990-2000	Methylprednisolone with low dose, alternative day prednisone and cytotoxics. Angiotensin converting enzyme inhibitor ± receptor blockade; vitamin E; ± plasmapheresis; ± cyclosporine (5 mg/kg/day).
Phase 4: 2000-2010	Angiotensin converting enzyme inhibitor (lisinopril 0.07 mg/kg/day, maximal 5 mg/day). Alternatively, an angiotensin receptor blocker (losartan 0.7 m/kg/day, maximal dose 50 mg/day). ± statin, ± vitamin E (200-400 units per day). ± mycophenolate mofetil (MMF 250-1200 mg/m ² /day; <2 gm/d, 2 divided doses), sirolimus (Rapamycin), tacrolimus (Prograf), or rituximab.

far outweighed the minimal benefits. However, in the decade from 1980 to 1990, low dose alternative day prednisone was used with or without addition of levamisole or cyclophosphamide. In the last decade of 1990 to 2000, methylprednisolone followed by tapering prednisone and cytotoxics, angiotensin converting enzyme inhibitors and/or receptor blockers and vitamin E, respectively, evolved as adjunct therapy.^{1,2}

Vitamin E

In the late 1990s, increasing evidence of oxidative injury in FSGS provided the rationale for use of the antioxidant vitamin E in FSGS treatment. The key study by Hahn et al,⁸ was designed to examine whether vitamin E can reverse established FSGS, which is similar to that of the clinical situations. Hahn et al⁸ showed that in experimental FSGS produced by the remnant kidney method, the glomerulosclerotic index was significantly higher in the FSGS compared to sham and pair-fed sham rats (Figure 1). The use of vitamin E resulted in a significant reduction in the glomerular sclerotic index, especially in view of the fact that the addition of vitamin E to the food was given two weeks after FSGS had been established in these rats. Previous studies always tested the effect of vitamin E given concurrent to the remnant kidney procedure – in effect, demonstrating the *preventive* effect of vitamin E and not the *reversal* of FSGS after it has been established, as would be the case in clinical practice. In addition, Figure 2 summarises the tubulointerstitial index, the plasma malondialdehyde (MDA) content, the kidney TGF- β mRNA and kidney MDA content: demonstrating the significant elevation of each of these parameters of oxidative stress and fibrogenic injury in FSGS. The use of vitamin E significantly reduces such indices of oxidative stress and

injury (Figures 1 and 2). We conclude that vitamin E can reverse established FSGS in this murine model of FSGS.⁸

The clinical efficacy of vitamin E in paediatric FSGS was examined in a study of Tabzib et al.⁹ In this study, all subjects received vitamin E capsules at 200 I.U. twice a day. Group A consisted of 11 children with biopsy-proven FSGS compared to Group B children with other kidney disorders. Group A subjects had significant reduction in

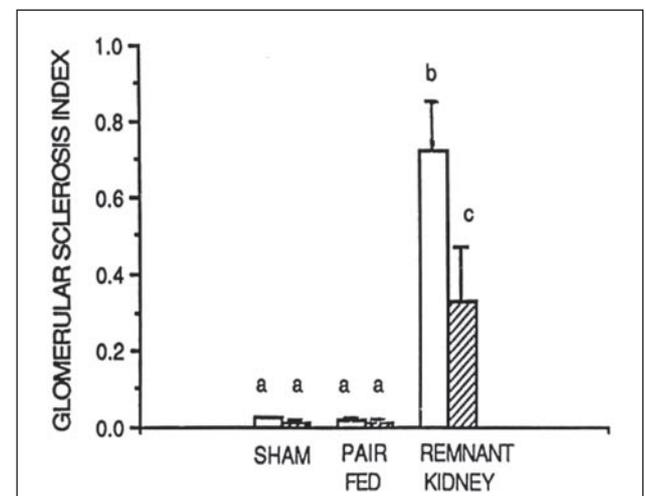


Figure 1 Glomerulosclerotic index. Each column represents the mean \pm SEM of data from six animals with FSGS produced by the remnant kidneys model. The data confirm a significant elevation in remnant kidney-FSGS compared with sham and pair-fed animals. α -Tocopherol treatment (stippled columns) of the remnant kidney groups significantly reduced the glomerulosclerosis. Different superscript letters indicate significant difference, $P < 0.05$. By permission from Hahn S, Kuemmerle NB, Chan W, et al. Glomerulosclerosis in the remnant kidney rat is modulated by dietary α -tocopherol. *J Am Soc Nephrol* 1998;9:2089-95.⁸

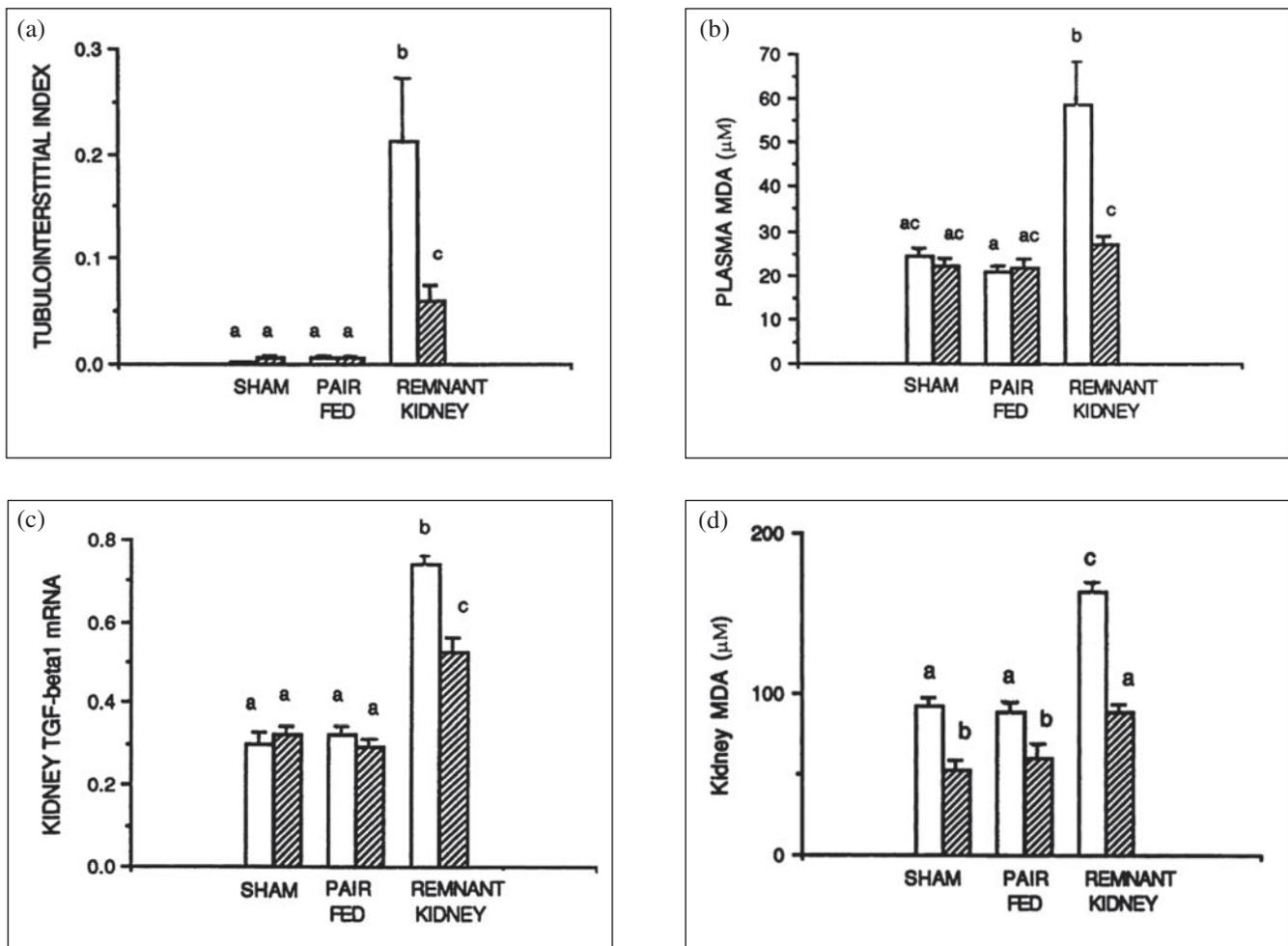


Figure 2 (a) Tubulointerstitial sclerotic index. Each column represents the mean \pm SEM of data from six animals with FSGS produced by the remnant kidneys model. The data confirm a significant elevation of the tubulointerstitial index in remnant kidney-FSGS compared with sham and pair-fed animals. α -Tocopherol treatment (stippled columns) of the remnant kidney groups significantly reduced the tubulointerstitial sclerosis. Different superscript letters indicate significant difference, $P < 0.05$. (b) Plasma MDA. α -Tocopherol treatment (stippled columns) of the remnant kidney groups significantly reduced the plasma MDA, suggesting a reduction in systemic oxidative stress. Different superscript letters indicate significant difference, $P < 0.05$. (c) Kidney TGF- β mRNA. α -Tocopherol treatment (stippled columns) of the remnant kidney groups significantly reduced the kidney TGF- β mRNA, suggesting a reduction of fibrogenic activities. Different superscript letters indicate significant difference, $P < 0.05$. (d) Kidney MDA. α -Tocopherol treatment (stippled columns) of the remnant kidney groups significantly reduced the kidney MDA, suggesting a reduction in intra-renal oxidative stress. Different superscript letters indicate significant difference, $P < 0.05$. By permission from Hahn S, Kuemmerle NB, Chan W, et al. Glomerulosclerosis in the remnant kidney rat is modulated by dietary α -tocopherol. *J Am Soc Nephrol* 1998;9:2089-95.⁸

proteinuria as shown by the dramatic reduction in urinary protein/urinary creatinine ratios from 9.7 ± 5.1 mg/mg to 4.1 ± 1.1 mg/mg ($P < 0.005$). Group B subjects showed no change in proteinuria. The limitations in this study are: 1) the open label study design, not a randomised, controlled clinical trial; 2) small number of children in each group; and 3) the short duration of treatment. Finally, the two groups are not strictly comparable in terms of their baseline severity of proteinuria.

Treatment Regimens

The evolution of treatment regimens is reflected in a single center study of 25 years in Virginia:¹ No therapy was used in the 1970s.^{1,6} But as the 1980s began, low dose prednisone, cyclophosphamide, cyclosporine, methylprednisolone were used. Later, angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blockade (ARB) and finally, vitamin E came into use.¹

Long-term Prognosis of SR-FSGS

Unfortunately, the long term prognosis of FSGS remains bleak, as illustrated in Figure 3. In the Virginia study,¹ with the evolving therapeutic regimens previously summarised,

the long-term prognosis represented by the kidney survival curve (A) of Figure 3, at a mean of 12 years of follow up, is that half of these children had progressed to end-stage kidney failure – no different than in the Toronto study,¹⁰ (D of Figure 3) in which the children received only cyclophosphamide and alternative day prednisone. In (B) and (C) of Figure 3, the short term studies of 4 years of follow-up from North Carolina,¹¹ showed that steroid-responsive and steroid-resistant FSGS patients demonstrated the expected good and bleak outcomes, respectively.

Efficacy Safety and Side-effects

Since the long-term outcomes of SR-FSGS are still discouraging, despite current therapeutic efforts, the safety and side effects of the multiple medications need to be compared (Table 3). Prednisone at low dose alternative day therapy minimises the growth retardation and other side effects of higher dose prednisone. Levamisole has been withdrawn from the US and Canadian market. Plasmapheresis is expensive. Its side effects include the various risks of blood products, thromboembolic risks, and suppression of immune system.

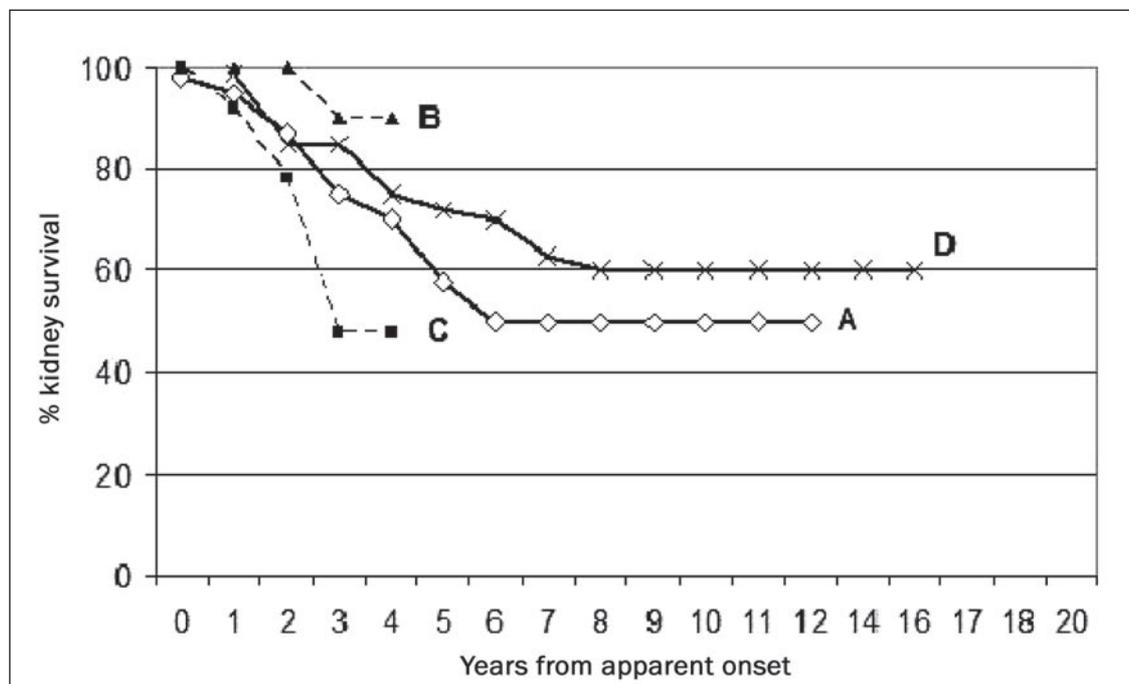


Figure 3 Long-term progression of FSGS. In (A) the Virginia study:¹ half of the study subjects progressed to end-stage kidney failure – no different than in (D) the Toronto study:¹⁰ the children received cyclophosphamide and alternative day prednisone. In (B) and (C), the short term studies from North Carolina¹¹ showed that steroid-responsive and steroid-resistant patients demonstrated good and bleak outcomes, respectively. By permission, from Chan JCM. Oxidative injury in focal segmental glomerulosclerosis. *Asian Biomed* 2008;2:19-26.

Table 3 Side effects of selected current therapeutic agents

Medication	Side effects
Prednisone and methylprednisolone	Euphoria, mood swings, headaches, acne, hirsutism, cushingoid facial appearance, fluid retention, hypertension, arrhythmia, and increased risk of infections, and diabetes mellitus. Long term use of high dose steroids gives rise to cataracts, osteoporosis, short stature.
Cyclophosphamide	Leucopenia from bone marrow suppression, haemorrhagic cystitis, and sterility.
Angiotensin converting enzyme inhibitor and receptor blockers	Allergic reaction, angioedema, coughing, anxiety, depression, dizziness, headache, fatigue, anaemia, vertigo, constipation or diarrhea, hyperkalaemia, urinary tract infection.
Statins	Muscle weakness, rhabdomyolysis, cognitive difficulty, neuropathy, liver enzyme elevation.
Cyclosporine	Pruritis, gum hyperplasia, hypertrichosis, neurological complications from confusion to seizures, gastrointestinal complications of nausea, vomiting, diarrhea, pancreatitis, peptic ulcers; hypertension, nephrotoxicity, hyperkalemia and other drug toxicities and interactions.
Levamisole	Allergic reactions, abdominal pain, nausea, and vomiting, neurologic complications from confusions to memory loss and seizures, bone marrow suppression and bleeding disorders.
Mycophenolate mofetil	Headaches, coughing, fatigue, thrombophlebitis, cytomegalovirus and opportunistic infections, anaemia, leucopenia from bone marrow suppression and gastrointestinal haemorrhage and perforation. Pregnant women should not take this medication because of fetal risks.
Sirolimus	Allergic dermatitis, acne, peripheral oedema, hypertension, arthralgia, gastrointestinal upsets, elevated serum triglycerides, cholesterol and creatinine, reduced glomerular filtration rate and proteinuria, and susceptibility to infections. When jointly used with cyclosporine, there is an increased risk of haemolytic uremia syndrome, thrombocytopenic purpura, and microangiopathy.
Tacrolimus	Increased risk of hepatotoxicity and nephrotoxicity, hyperglycemia, diabetes mellitus, hypertension, neuropathy, blurred vision, tremors, seizures, confusion, insomnia and herpes zoster infections.
Rituximab	Runny nose, sneezing, throat irritation, nausea or vomiting, abdominal pain, headache, skin rash, muscle weakness, muscle or joint pain, night sweats. This anti-CD20 monoclonal antibody incurs an increased risk of opportunistic infections, arrhythmia, respiratory distress, hypotension.

Combined Therapy in SR-FSGS*a) Methylprednisolone; alkylating agents; cyclosporine*

Pulse intravenous methylprednisolone¹² carries a relatively high risk of cataracts, hypertension, growth retardation and infectious episodes (Table 3).¹³ Alkylating agents are often no more effective than low dose prednisone. Cyclosporine is now the standard of care in SR-FSGS.³ But cyclosporine nephrotoxicity and dependency are unsettled issues.

b) Plasmapheresis; calcineurin inhibitors

Primary FSGS arises from multiple defects.³ The mutation of podocyte structural protein is coupled with elevated circulating permeability factors (PF), increasing glomerular leakage. Plasmapheresis functions by removing

this PF, but does not repair the defective cytoskeletal structure of the podocytes. It remains for the calcineurin inhibitors to stabilise the cytoskeletal structure of the podocytes.

c) Tacrolimus; sirolimus

Segara et al¹⁴ used tacrolimus coupled with tapering prednisone treatment. The results have been encouraging. Sirolimus, an analogue of tacrolimus, may have less nephrotoxicity, but the same troubling side effects of anaemia, hyperlipidemia and oral ulcers. Furthermore, tacrolimus plus prednisone combined therapy is still limited by the small number of patients studied and the short term follow ups.¹⁵ There is continuing lack of randomised, controlled clinical trials with enough statistical power.

d) Mycophenolate mofetil (MMF)

Barietta et al¹⁶ reported a study on a number of renal patients treated with MMF, but showed only two children with SR-FSGS in this cohort: one child suffered two relapses 12 months before and no relapses 12 months after MMF; but the other child suffered three relapses in the 12 months before MMF treatment and continued unchanged with three relapses in the same period afterwards. Similarly, Choi et al¹⁷ reported a cohort of patients treated with MMF. Out of this cohort, the two patients with SR-FSGS did not suffer relapses on complete steroid withdrawal, 6 to 8 months after discontinuation of MMF. Although somewhat encouraging, the reports are ultimately disappointing, because each of these short-term, uncontrolled studies were based on only two SR-FSGS patients, respectively. Finally, both reports did not mention the actual or potential side effects of MMF, which include oral ulcer, anaemia, hyperlipidemia, and nephrotoxicity.

e) Lisinopril, Losartan plus MMF

Montane et al¹⁸ studied a combination therapy of lisinopril, losartan plus MMF in nine children with SR-FSGS. Their age averaged 9±5 years. After 6 months of this combined therapy, urine protein/creatinine showed a reduction of 72% from baseline. Hypercholesterolemia was also significantly lowered.

In a follow-up study from this same group, Hubsch et al,¹⁹ reported the use of lisinopril, losartan plus MMF in ten kidney allograft, biopsy-proven recurrent FSGS. After 27±15 months of treatment with this combined therapy, proteinuria achieved a 94±8% reduction from baseline.

ClinicalTrials.gov

Since the previous studies have been published more than 5 years ago,¹⁶⁻¹⁹ the results of additional trials in the interval were searched from the web-site, ClinicalTrials.gov. We found a total of 19 trials, registered from the US and other parts of the world. It has become the policy of almost all journals to require any clinical trial submission

for consideration of publication, to provide evidence that they have registered with this central organisation, in order to ensure open, public access. Our search showed that in general, the study designs consist of variations of combining: 1) low dose prednisone up to 2 years; 2) adjunct therapies of rosiglitazone, adalimumab, rituximab, dexamethasone, MMF, tacrolimus or sirilimus. No outcome data have been otherwise reported, even those indicating that study has been completed, with the exception of the following reports by Middleton et al,²⁰ and Trachtman et al.^{21,22}

a) Cyclosporine versus MMF and Dexamethasone

A search of ClinicalTrials.gov on FSGS involving paediatric patients showed a study by Middleton et al²⁰ entitled FSGS-CT. Cyclosporine was compared to MMF plus dexamethasone. Currently, 192 children and young adults have been enrolled into the study. Hypertension has commonly been encountered and was difficult to control. A second report from the same FSGS-CT study by Trachtman et al²¹ showed that the quality of life (physical, emotional, social and school function) scores were low in SR-FSGS patients and close to the low scores of chronic kidney disease patients.

b) Galactose versus Adalimumab

Finally, Trachtman et al²² compared adalimumab versus galactose in two groups of FSGS patients, who were otherwise maintained on lisinopril; losartan; statin; rosiglitazone. First, they showed that 30% of FSGS patients demonstrated the presence of circulating permeability factor – which most likely increased glomerular albumin permeability. On the rationale that galactose binds this factor, treatment with galactose should lower albuminuria. Accordingly, in this study, biopsy-proven, steroid resistant FSGS patients with permeability factor >0.5 were given oral galactose: 0.2 g/kg/dose twice a day for 28 days. The proteinuria and the permeability factor dropped significantly in the galactose-treated patients. If this study is confirmed by others, galactose may become the adjuvant therapy of choice in SR-FSGS.

Table 4 Genetic defects in familial FSGS

Autosomal dominant FSGS	Defect in chromosome 19q13; 11q21-q22: mutation α actin-4
Autosomal recessive FSGS	Defect in chromosome 1q25-q31 Mutation of causative gene NPHS2 expressed on podocytes: integral membrane protein, podocin. Podocin mutation identified in up to 30% patients with sporadic steroid resistant nephrotic syndrome. CD2AP anchors CD2 receptor of T lymphocytes to cytoskeleton also expressed in podocytes.

Steroid-resistant FSGS and Mutations of Causative Genes

Of importance in understanding nephrotic syndrome is that of the integrity of the slit diaphragm is disrupted. This slit diaphragm is under the control of at least two genes: nephrin and NEP1. Secondly, membrane integrity is interrupted in nephrotic syndrome, which is under the control of podocin²³ and CD2AP. Finally, cytoskeleton integrity is impaired in nephrotic syndrome, which is under the control of actinin 4.

The central role of podocytes can be gleaned from knockout studies. Podocin knockout mice developed defective glomerular basement membrane, resulting in massive proteinuria. These animals do not survive. They die of kidney failure shortly after birth.

Mutation of INF2 on chromosome 14q in autosomal dominant and autosomal recessive FSGS patients has led to several observations, including mutation of causative gene NPHS2 expressed on podocytes and the integral membrane protein, podocin^{23,24} (Table 4). Molecular alteration in podocin gene (NPHS2)²⁵⁻²⁷ plays a critical role in familial FSGS. There is also evidence on the missense of TRPC 6 cation channel in the genesis of FSGS.

Podocin mutation has been identified in up to 30% of patients with sporadic steroid resistant nephrotic syndrome. CD2AP anchors CD2 receptor of T lymphocytes to cytoskeleton in podocytes.

Pierson syndrome of congenital nephrosis has been linked to LAMB2 mutation. Denys-Drash syndrome and Frasier syndrome both are linked to WT1 mutation. Finnish type, congenital nephrotic syndrome²⁸ is linked to mutation of NPHS-1, isolated in chromosome 19.

In summary, the genes and linkages associated with familial FSGS are beginning to be identified (Table 4). In the recent decade, our understanding that increased permeability factor as a central mechanism in FSGS is just beginning to be explored. Mutation of genes and elevated circulating permeability factor, contribute to development of recurrent FSGS in kidney allograft.

Conclusions

We have come a long way from 1970s, when no treatment was recommended for SR-FSGS due to lack of response to multiple therapeutic approaches. Still, long-term, favourable prognosis for SR-FSGS remains bleak. Standard treatment consists of:

- Lisinopril;
- Losartan;
- Statin;
- Vitamin E for proteinuria less than 2 gm/day; and
- Cyclosporine for proteinuria over 2 gm/day.

Combined therapeutic regimens using non-steroidal agents, angiotensin converting enzyme inhibitor or receptor blocker,²⁹ antifibrotic agents and/or cytotoxics, and galactose have been attempted. Limitations of these clinical investigations are the inadequate patient populations, the short follow-up period, adverse side effects, and safety considerations.

Despite many advances, the long-term prognosis of SR-FSGS is still poor. Thus research into novel therapy is required. Future studies into the genetics of familial FSGS may lead to specific cell-based therapy and a brighter future for patients with this condition.

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