Treatment of FSGS in Children

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Focal segmental glomerulosclerosis (FSGS) is a pathologic condition that represents many disease entities. The goals of therapy are to cure the disease. When this is not possible, the secondary goals are to reduce proteinuria to avoid the complications of nephrotic syndrome and to delay progression of kidney disease. Proteinuria remission is one of the most important independent predictors of kidney survival. Children with FSGS who do not achieve partial or complete remission have a 50% risk of progression to ESRD within 5 years whereas those who enter complete remission have a 5-year kidney survival rate of 90%. Treatment of idiopathic FSGS commonly involves immune-based and nonimmunologic therapy options. This manuscript will review the current state of FSGS therapy for children.

Key Words: FSGS, Child, Nephrotic syndrome, Therapy

Introduction

Focal segmental glomerulosclerosis (FSGS) is a pathologic condition that represents many disease entities, including genetic and nongenetic forms. We remain in the discovery phase when considering disease causes, disease modifiers, and patient-specific therapies. Given our immature knowledge, we find ourselves reliant on therapies that have been in the standard-of-care realm while seeking drugable-targets. This manuscript will review the disease phenotypes and standard therapies and outline the current progress toward the future state of precision medicine in FSGS. A companion manuscript (Trachtman and colleagues in this issue) describes novel approaches to treatment-resistant disease.

Presentation

Infants and children are at risk for FSGS. Children with FSGS may present with asymptomatic proteinuria discovered during routine health screening such as an annual or sports physicals. Those with the full nephrotic syndrome presentation may come to attention because of severe progressive edema. Alternatively, when FSGS is secondary, the presence of proteinuria may be identified as a complicating factor within another health condition. On urinalysis, proteinuria is the predominant finding. Quantitative measures of proteinuria reveal a wide range of values of 0.5 to over 20 g of protein excretion per day. Painless hematuria may be present in microscopic or rarely macroscopic levels. Dyslipidemia is commonly present and may be proportional to the degree of hypoalbuminemia and proteinuria. Hypertension is present in approximately 1/3 of children at presentation.

FSGS may arise as a result of a monogenetic polymorphism with or without a family history of disease. Neonates and infants with nephrotic syndrome have a high likelihood of a monogenetic disorder. In a study from an international cohort, 85% of neonates and 44% of infants with new-onset nephrotic syndrome were attributed to mutations.[1] In these cases, genetic testing and subsequent examination of kidney tissue will distinguish cause and histopathology. Some of the genetic disorders resulting in FSGS are associated with syndromic features that alter prognosis and define the diagnosis and monitoring approach, such as Denys Drash and Frasier Syndrome with *WT1* polymorphisms and increased risk for nephroblastoma and gonadoblastoma.[2] Consequently, in the setting of congenital and infantile nephrotic syndrome or syndromic disease with proteinuria, genetic testing may be considered a part of the routine evaluation. Older children and adolescents have a lower prevalence of monogenic causes of FSGS. International studies have a substantial influence of consanguinity, which makes these results difficult to generalize across populations with diverse ancestry. In sporadic cases of disease without a history of consanguinity, 6% of adolescents with steroid-resistant nephrotic syndrome (SRNS) have been found to have a podocin-associated disease.[3] African-American children appear to have a lower prevalence of podocin mutations.[4] Conversely, African Americans have a higher prevalence of *APOL1* polymorphisms, which have been associated with a greater risk for FSGS disease progression in adults.[5]

Secondary FSGS may be caused by prior kidney insults from infections, nephrotoxic drug exposure, cancer, and previous inflammatory insults. A low nephron number such as is seen in unilateral kidney agenesis or prior surgical resection may result in secondary FSGS, but this is more commonly observed in older adolescents or adults. Prematurity and obesity are risk factors for FSGS and progressive kidney disease.[6] Weight loss in the obese patient provides a therapeutic target with an advantageous risk/benefit profile.

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Diagnosis

The ultimate diagnosis of FSGS is based on kidney biopsy findings that include a distinct pattern of scarring. In idiopathic FSGS, the biopsy often includes effacement of the podocytes, which may be absent or a minor finding in secondary cases. Classification of FSGS into distinct pathologic patterns has been defined and published as the Columbia Classification.[7] The Perihilar, Tip, Collapsing, and Cellular variants are individually less common than the "Not Otherwise Specified" classification. The risk for progression to end-stage kidney disease (ESKD) appears to be worse for those with Collapsing variant disease and better for Tip lesion variants compared with other FSGS variants in children and adults with steroid-resistant, idiopathic FSGS.[7]

Treatment

Treatment of FSGS in children can often prove to be challenging because of the paucity of large-scale, randomized controlled trials that provide robust evidence to guide therapy. The goals of therapy are to cure the disease. When this is not possible, the secondary goals are to reduce proteinuria to avoid the complications of nephrotic syndrome and to delay progression of kidney disease. Proteinuria remission is one of the most important independent predictors of kidney survival (Table 1). Children with FSGS who do not achieve partial or complete remission have a 50% risk of progression to ESRD within 5 years, whereas those who enter complete remission have a 5-year kidney survival rate of 90%.[8-10]

CLINICAL SUMMARY

- Treatment options for primary FSGS includes immune- and nonimmune-based therapies.
- Treatment for secondary FSGS includes treatment of the primary disease and FSGS progression prevention strategies such as blood pressure and fibrosis control.
- The future of FSGS therapy will include individualized target-based therapy.

Treatment of idiopathic FSGS typically involves immune-based and nonimmunologic therapy aimed at reducing proteinuria, although no standard treatment protocol currently exists. Preferences on class and sequencing of immunomodulatory drugs for the treatment of FSGS have varied over time and by region. There are conflicting reports about the effectiveness of immunosuppression therapy in FSGS associated with genetic mutations, but the response rate is generally considered to be poor.[11,12] In secondary forms of FSGS, treatment is targeted at the underlying cause.

Therapy

Corticosteroids

Corticosteroid therapy is the mainstay of treatment for idiopathic nephrotic syndrome in childhood. Most children presenting with primary nephrotic syndrome have minimal change disease, which typically responds to corticosteroids[13]; therefore, most pediatric nephrologists will empirically treat nephrotic children without a kidney biopsy. Standard treatment is with oral prednisone at a dose of 60 mg/m^2 or 2 mg/kg daily for 4 to 6 weeks followed by 40 mg/m^2 or 1.5 mg/kg every other day for 4 to 6 weeks.[14] In the International Study of Kidney Disease in Children study, approximately 1/3 of 37 patients with FSGS demonstrated a response to steroids.[15] Likewise, 29% (16 of 56) of children with FSGS in the Southwest Pediatric Nephrology Study Group were found to be sensitive to steroids.[16]

Approximately 10% to 20% of children with idiopathic nephrotic syndrome fail to respond to corticosteroids, most of who have FSGS.[13] There is debate about the optimal dose and duration of therapy, but the lack of response to treatment after 8 weeks generally defines steroid resistance.[17] However, there have been instances of late remission with prolonged or high-dose corticosteroid therapy. In the control arm of a clinical trial that included 60 children with steroid-resistant FSGS, 25% of patients treated with alternate-day prednisone at 40 mg/m^2 for 12 months entered into remission.[18] A 2-week course of intravenous pulse corticosteroids induced remission in approximately 1/3 of 81 patients with SRNS, including 41 with FSGS.[19] However, it is unclear from the data how many with FSGS responded to treatment. In addition, in a retrospective study of 52 children with steroid-resistant FSGS, those treated with cyclosporine plus intravenous methylprednisolone had higher rates of complete remission compared with those given cyclosporine plus oral prednisone (84% vs 64%).[20] These 2 studies included populations not representative of children with FSGS in North America.

Although FSGS is largely considered to be resistant to steroids, corticosteroids have traditionally been retained as an element of many therapeutic protocols for FSGS, usually in combination with various other drugs such as calcineurin inhibitors. Nonetheless, the significant side effects of prolonged corticosteroid therapy need to be taken into consideration. These include hypertension, growth impairment, immune suppression, diabetes mellitus, weight gain, cataracts, behavioral changes, sleep disturbance, concentration challenges, psychosis, and osteoporosis. These side effects have led to the preference for lower corticosteroid doses, shorter courses, and regimens without concomitant corticosteroids in the clinical setting.