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"Presumed" Primary Focal Segmental Glomerulosclerosis: A Novel Nuance for Steroid Therapy

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Treatment of a light microscopic (LM) lesion of focal segmental glomerulosclerosis (FSGS) discovered in a kidney biopsy specimen in a patient with proteinuria has been shrouded in controversy for decades. This veil of uncertainty has been partially lifted by the recognition that the lesion of FSGS is quite heterogeneous in etiopathogenesis and that a subset, often called primary FSGS, can be presumed based on a combination of clinical and histopathologic characteristics.[1] This subcategory of FSGS is believed to have an etiopathogenesis linked to a posited circulating permeability factor (or factors) causing widespread podocyte malfunction and increased glomerular permeability to plasma proteins. The identity of such factors is largely unknown, although several candidates have received much attention.[2] Furthermore, we still lack a definitive serum or urinary biomarker with high sensitivity or specificity for primary FSGS. Steroid or immunosuppressive therapy is largely ineffective in the secondary and genetic forms of the FSGS lesion and highly uncertain in the lesion of FSGS of undetermined etiopathogenesis.[3]

Previous interventional studies in patients with a FSGS lesion have suffered greatly from a deficiency related to poor characterization of phenotypes resulting in a mixed population of patients being enrolled in such studies (e.g., the diagnosis of primary FSGS cannot be fully achieved by renal biopsy alone). A further limitation is the paucity of well-controlled randomized trials of treatment.[3] Patients with a lesion of FSGS, thought to represent primary FSGS ("presumed" primary FSGS), have often been empirically characterized as steroid responsive, frequently relapsing/steroid-dependent, or steroid resistant based on the time-related reduction in proteinuria level observed after initiating treatment with corticosteroids and its duration after dose reduction or discontinuation. Although, in children, steroid resistance is defined as no response after 4 to 8 weeks of therapy with high-dose corticosteroids,[4] no consensus exists in adults. Furthermore, little attention has been given to the evolution of quantitative proteinuria during therapy as a predictor of treatment responsiveness and long-term outcomes.

These deficits in the existing literature have been, in part, remedied by a retrospective, observational cohort study conducted by Rood *et al*.[5] published in this issue of the *KI Reports*. Patients enrolled were referred to a single center in Nijmegen, The Netherlands, between 1995 and 2014 and followed for at least 6 months unless they died or developed kidney failure within 6 months. All patients included in the cohort ($n = 51$) were treated with high-dose corticosteroids as monotherapy (usually initiated within approximately 2 months after kidney biopsy) and had persistent proteinuria (partial remission [PR] or no change from baseline levels) 8 weeks after initiation of steroid therapy. Concomitant renin-angiotensin inhibitor therapy was used in 94% of the selected cohort.

All patients were adults (average approximately 46 years) and "presumed" to have primary FSGS based on clinical criteria (nephrotic syndrome, i.e., proteinuria level ≥3.5 g/d or ≥3.5 g/10 mmol creatinine and a serum albumin level of ≤3.0 g/dl, absence of known secondary causes, or a family history of kidney disease). Diffuse podocyte foot process effacement by electron microscopy was present in 27 of 29 cases (93%) evaluated, but only 57% of the total cases had electron microscopy performed, pointing to a potential limitation of the study. The distribution of the

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morphologic variants of the FSGS lesion by LM was typical: 49% with "not otherwise specified"; 40% with "tip"; 3% with collapsing; and 1% with "cellular" lesions. No perihilar variants were observed. Genetic analyses were performed in 25 of 51 patients: 6 in routine practice and 19 in the context of a research protocol. In addition, there were 8 patients who were classified as primary nonresponders. Of these, 7 underwent genetic analysis that identified 2 cases of genetic FSGS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS] and 1 *NPHS2* compound heterozygote; 2 of 7; 28.5%).[5] The initial median serum creatinine level of the entire cohort was 1.07 mg/dl (interquartile range = 0.88–1.60 mg/dl), and the 24-hour urine protein or gram per 10 mmol was 8.5 g (interquartile range = 6.4–12.2 g). Serum albumin level was approximately 2.0 ± 0.5 g/dl.

The results are very illuminating. Only 20% of the patients (10 of 51) had a PR at 8 weeks. Corticosteroid therapy was continued after 8 weeks in reduced dosage, and some patients received additional therapy (calcineurin inhibitor [CNI], rituximab, cyclophosphamide, or azathioprine). The cumulative per patient exposure to steroids was 11,440 mg. At 16 weeks, 16 of 51 cases (31%) had developed a PR and none had developed a complete remission (CR). At 24 weeks, 23 of 51 cases (45%) had developed a PR with 1 having CR. Overall, 27 of 51 cases (53%) obtained a PR or CR with continued corticosteroid therapy without concomitant use of additional therapy (CNI or rituximab). There were 22 patients who had ≥1 relapses, more often after PR than CR. Late nonresponders after initial PR were found in 5 of 14 patients.

In long-term follow-up (median: 7.1 years), 7 patients developed kidney failure—all primary or secondary nonresponders. Overall renal survival was 92% and 64% at 3 and 10 years, respectively. Outcomes could be predicted by the initial response to steroids during the period from 0 to 8 weeks, that is, >20% reduction of proteinuria level. Only 1 of 24 patients (4%) with such an initial decrease of proteinuria level was unresponsive (PR or CR) on continuation of steroid or additional therapy. Nevertheless, 7 of 10 patients (70%) without such an initial decrease in proteinuria level remained nonresponsive to any therapy. Approximately 63% of the patients who were responsive to steroids (or some additional agents) had stable renal function (<15 ml/min per 1.73 m^2 decrease in estimated glomerular filtration rate during follow-up). Greater degrees of functional deterioration were found in those who received CNI as additional therapy. The nonresponder population tended to be much younger (median age: 29.3 years; interquartile range = 19–34 years) and had a greater risk of developing kidney failure during the follow-up.

Although observational in design, the study provides some new insights to steroid therapy of "presumed" primary FSGS. Primary FSGS is a clinical–pathologic diagnosis that cannot be confirmed by any currently available biomarker. The LM pattern of the FSGS lesion is of little diagnostic, prognostic, or therapeutic utility, except perhaps when a "peri-hilar" pattern is observed, which should signal the possibility of a nonprimary lesion.[1,3] In this cohort, selected on the basis of no CR at 8 weeks, the LM subtype was of no help in predicting subsequent response or long-term outcome. Although patients who achieved a CR at <8 weeks were excluded from the cohort, there were only 2 such cases.

In this study, the likelihood of finding a monogenic cause of FSGS which responded to immunosuppression therapy was low (<8%) and similar to recent studies.[6] Nevertheless, the high rate of genetic mutations found in patients who fail to respond to immunosuppressive therapy (28.5%) points to the need for doing genetic analysis in such cases.[7] The overall response rate to steroids or adjunctive agents of patients with presumed primary FSGS (after excluding genetic FSGS) was high, approaching 80%.

The definition of "steroid resistance" in adults with "presumed" primary FSGS needs to be reconsidered. CRs can develop in up to 40% of patients with prolonged follow-up and application of adjunctive therapy. Furthermore, PR is also not a good marker of treatment responsiveness because 31% of the patients in this cohort developed at least 1 PR within 16 weeks, but overall, 80% developed a PR at some time during the follow-up. As such, the response to corticosteroids in "presumed" primary FSGS varies considerably with respect to the duration of treatment. Some patients respond quickly with a CR (and often with ≥1 relapses), whereas others require very prolonged treatment, often involving adjunctive agents (such as CNI). The key observation that even a modest reduction (>20% from baseline) in proteinuria level after 8 weeks of therapy can signal later responsiveness is a useful biomarker for predicting overall responsiveness to therapy in clinical practice, but further studies are needed to confirm this proposition. Failure of proteinuria level to decrease >20% from baseline after 8 weeks of high-dose corticosteroid treatment should

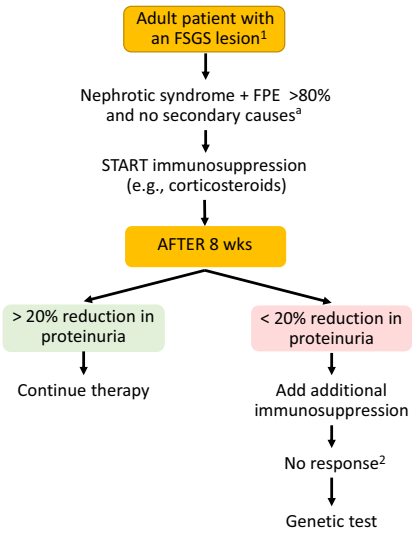

Figure 1. A proposed therapeutic and genetic testing algorithm. [a]No family history of kidney disease, viral illnesses, drugs/toxins, autoimmunity, and malignancy. [1]This algorithm applies to patients initially treated with steroids only and limits adjunctive therapy to Calcineurin inhibitors, Rituximab or Mycophenolate Mofetil. Cyclophosphamide is not recommended for treatment-resistant monogenic focal segmental glomerulosclerosis (FSGS). [2]No response after adding additional adjunctive immunosuppressive agents is suggested by failure to reduce proteinuria more than 20% after 8 weeks. FPE, foot process effacement.

raise consideration for initiating secondary immunosuppressive therapy[8] (Figure 1). This study also signals concern on using CNI for adjunctive therapy of "presumed" primary FSGS, as renal functional deterioration is more common in CNI-treated patients. As such, early withdrawal of CNI in patients with deteriorating estimated glomerular filtration rate should be given careful consideration.

Finally, very appropriately, the authors draw attention to the potential adverse effects of long-term exposure to high-dose steroids.[9] Although adverse events were not systematically recorded in this retrospective study, it seems reasonable to suggest that alternative treatment regimens, such as initial treatment with CNI monotherapy, be considered when risks of steroid-related side effects are judged to be elevated and to attempt steroid minimization therapy when intolerable steroid-related side effects become apparent.

This study is important for the following reasons:

1. It reveals that long-term success can be achieved in many patients with "presumed" primary FSGS by judicious use of steroids and adjunctive therapy with other agents.
2. A genetic cause of the FSGS lesion will seldom be found in adult patients categorized with having "presumed" primary FSGS by proper clinicopathologic criteria (i.e., nephrotic syndrome and widespread foot process effacement on electron microscopy), except in patients who are resistant to corticosteroids and additional immunosuppressive therapy.
3. Evaluation of LM subvariants of the FSGS lesion is of little help in phenotyping a patient with "presumed" primary FSGS and of no prognostic benefit in adult patients having steroid resistance after 8 weeks of treatment.
4. The definition of "steroid resistance" in adults with "presumed" primary FSGS is much more nuanced than the absence of a CR or PR at any given point in the observation after initiating steroid treatment.
5. The use of CNIs as adjunctive therapy for steroid-resistant "presumed" FSGS is a "two-edged sword" having both short-term beneficial and longer-term harmful aspects, particularly in young subjects with initially normal glomerular filtration rate and those with underlying renal fibrosis.
6. More refined and nuanced ways to identify the true nature of "presumed" primary FSGS are needed to more efficiently categorize the steroid-sensitive and steroid-resistant forms of primary FSGS.[3] Perhaps a panel biomarker analysis would help to better characterize patients with "presumed" primary FSGS.[S1]

DISCLOSURE

RJG reports receiving consulting fees from Bristol-Myers Squibb, ChemoCentryx, Omeros, Ionis, Travere, Horizon, BioCryst, Equillion, Aurinia, Calliditas, RenaSight (Natera), Novartis, River3Renal, Foresee Pharmaceuticals, Otsuka, Anteris, Therini, NephroSys, Chinook, Arrowhead, and Alexion; receiving editorial stipends from UpToDate (Wolters-Kluwer) and Karger; and serving as a member of the Speakers Bureau for Aurinia. FCF reports receiving editorial stipends from UpToDate (Wolters-Kluwer).

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Reference.

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