

Rethinking First-Line Immunosuppression for Idiopathic FSGS

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FSGS represents a common histopathologic end point for a diverse group of underlying disease processes (1). These include adaptive and structural changes to the glomeruli, as seen in patients with reflux nephropathy, solitary kidney, low nephron mass, hypertension, and obesity (2), and direct injury to podocytes as occurs with HIV-associated nephropathy, drug exposures, and genetic mutations (2,3). Idiopathic FSGS is diagnosed when a patient presenting with proteinuria (commonly nephrotic range) exhibits FSGS on kidney biopsy, with no clear contributing (*i.e.*, secondary) etiology. This is an important distinction, because it may prompt the use of immunosuppression to attain a remission in proteinuria. Spontaneous remission for patients with idiopathic FSGS and nephrotic-range proteinuria is rare (4), and progression to CKD and ESRD is common for patients who do not experience remission of proteinuria (5). Steroid-resistant FSGS is one of the most challenging glomerular diseases to manage. Although there is evidence that some patients have idiopathic FSGS that is caused by a yet unidentified circulating permeability factor (6–8), it is likely that idiopathic FSGS represents multiple, diverse, and poorly understood pathophysiologic mechanisms.

There is minimal understanding of the mechanisms by which pharmacologic treatments affect disease progression in idiopathic FSGS. The Kidney Disease Improving Global Outcomes practice guidelines for glomerulonephritis recommend renin-angiotensin-aldosterone system blockade, and for patients with nephrotic-range proteinuria, initiation of high-dose glucocorticoid therapy (1 mg/kg daily or 2 mg/kg on alternating days) as first-line therapy (3). Calcineurin inhibitors (CNIs) may be considered in patients with relative contraindications to high-dose steroids (3). These recommendations are primarily on the basis of small retrospective case series (4,9–15), the largest of which comprised 53 patients (10). Although randomized, controlled trials have compared the effectiveness of therapies for steroid-resistant FSGS, data comparing first-line glucocorticoids with other potential first-line therapies are extremely limited (16–18).

In this issue of the *Clinical Journal of the American Society of Nephrology*, Laurin *et al.* (19) present an analysis of the largest cohort of patients with idiopathic FSGS to date. Using the Glomerular Disease Collaborative Network (GDCN) Registry, Laurin *et al.* (19) showed that early treatment with any immunosuppression was

associated with significantly greater renal survival compared with no immunosuppression in 458 adults and children with FSGS (hazard ratio, 0.49 for ESRD; 95% confidence interval [95% CI], 0.28 to 0.86). There was no significant difference in renal survival among patients treated with glucocorticoids alone compared with patients treated with CNIs, although there was a trend toward greater survival among patients treated with CNIs.

This study provides important insight into the effects of immunosuppressive therapy on renal outcomes in these patients. It is, by far, the largest observational study evaluating the treatment of idiopathic FSGS with early immunosuppressive therapy. It is the first study of its size to compare renal outcomes between patients treated with early glucocorticoids alone and those treated with early CNI therapy. Perhaps most importantly, the study provides higher-quality evidence than was previously available to support the use of early immunosuppression to prevent ESRD in these patients. Another unique aspect of this study is the light that it sheds on practice patterns. Immunosuppression was prescribed more often in patients with tip lesion FSGS (odds ratio [OR], 3.0; 95% CI, 1.23 to 7.32 versus patients with FSGS not otherwise specified), preserved eGFR (OR, 0.53; 95% CI, 0.29 to 0.99 for eGFR <30 ml/min per 1.73 m²), and hypoalbuminemia (OR, 2.2 for each 1 g/dl lower; 95% CI, 1.59 to 3.13). CNIs were less likely to be prescribed for patients with tip lesion FSGS. Because management was left to the discretion of >600 referring physicians in eight states in the GDCN, these observations likely reflect real life patterns in the treatment of patients with FSGS between 1980 and 2012.

Laurin *et al.* (19) also used a type of survival analysis that takes into account changes in medication exposure over time, allowing for patients to crossover between treatment groups. The methodology is a practical approach to address a common occurrence in clinical practice that has the potential to heavily bias the results of an observational study. However, the time-varying Cox survival modeling used in the study is also prone to bias. Although the analyses adjusted for factors that were found to be confounders for initial selection of therapy, the effects of confounders that change over time, such as eGFR and proteinuria (*i.e.*, markers of remission), were not addressed, which may play an important role in both changes in therapy and the

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rate of development of ESRD (20,21). Follow-up proteinuria data, in particular, was often missing (64%). As a result, proteinuria could not be reliably used as an outcome measure; the analyses describing the clinically important outcomes of complete and partial remission were inconclusive. Additionally, the analyses of practice patterns do not take into account changes over time as clinical practice guidelines evolved. Finally, the observed trend toward improved renal survival in patients treated with CNIs compared with glucocorticoids alone requires more intensive, prospective investigation before changing current practice.

The most important limitation for all studies in idiopathic FSGS is that the diagnosis is made on a clinicopathologic basis rather than according to pathogenesis. It is likely that multiple mechanisms are responsible for the development of proteinuria and the FSGS lesion. Although the study by Laurin *et al.* (19) adds to the epidemiologic data on the management of idiopathic FSGS, the mechanistic role of immunosuppression in the management of idiopathic FSGS remains unclear. As a field, we hope that basic and clinical research in glomerular diseases, including large cohort studies, such as the Nephrotic Syndrome Study Network and Cure Glomerulonephropathy, will lead to the (re) grouping of patients with FSGS on the basis of mechanism and therapeutic implications. The reclassification of idiopathic membranous nephropathy on the basis of anti-phospholipase A2 receptor antibody status is the model that we strive to emulate (22). Until that occurs, the study by Laurin *et al.* (19) is a much-needed, well designed affirmation of the current management of idiopathic FSGS.

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Disclosures

None.

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See related article, “Treatment with Glucocorticoids or Calcineurin Inhibitors in Primary FSGS,” on pages 386–394.